ClinicalEvidence

Bipolar disorder

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ABSTRACT

INTRODUCTION: Bipolar disorder, with mood swings between depression and mania, may affect up to 1.5% of adults, and increases the risk of suicide and disability. Most people improve over time, but two thirds may have residual dysfunction, and at least 40% may have recurrent episodes. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments in people with mania associated with bipolar disorder? What are the effects of treatments in bipolar depression? What are the effects of interventions to prevent relapse of mania or bipolar depression? We searched: Medline, Embase, The Cochrane Library and other important databases up to July 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 60 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antidepressants, carbamazepine, chlorpromazine, clonazepam, cognitive therapy, education, family-focused psychoeducation, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, psychological treatments, quetiapine, risperidone, topiramate, valproate, and ziprasidone.

QUESTIONS

INTERVENTIONS

Key points

- Bipolar disorder, with mood swings between depression and mania, may affect up to 1.5% of adults, and increases the risk of suicide and disability.

  Most people improve over time, but two thirds may have residual dysfunction, and at least 40% may have recurrent episodes.

- Lithium reduces symptoms of mania compared with placebo, and seems as effective as haloperidol, carbamazepine, and clonazepam, but can cause adverse effects including hypothyroidism.

- Older antipsychotic drugs such as chlorpromazine and haloperidol are widely used to treat mania, but few studies have been done to confirm their efficacy.

  Olanzapine, valproate, carbamazepine, and risperidone increase the likelihood of response in people with mania compared with placebo, and seem to have similar efficacy as each other, with different adverse-effect profiles.

  Ziprasidone, quetiapine, and clonazepam may also be beneficial, but few studies have been done to assess the effects of lamotrigine or gabapentin in mania.

  Topiramate is unlikely to be beneficial in mania.

  Antidepressants increase treatment response compared with placebo in people with bipolar depression. It is possible that selective serotonin reuptake inhibitors are more effective, and less likely to induce mania, compared with tricyclic antidepressants.

  Lamotrigine may increase response rates in people with depression compared with placebo, but can cause headache.

  Quetiapine may also improve depression compared with placebo.

  We don't know whether lithium, carbamazepine, valproate, or topiramate improve depression in people with bipolar disorder.

  We don't know whether psychological treatments are effective for people with bipolar depression, as we found no studies.

- Lithium reduces relapse in bipolar disorder compared with placebo.

  Valproate, carbamazepine, and lamotrigine seem as effective as lithium in reducing relapse.

  Cognitive therapy and patient or family education may reduce the risk of relapse, but studies have given conflicting results.

  We don't know whether antidepressants can prevent relapse, and they may induce mood instability or manic episodes.

  Olanzapine may reduce relapse, but long-term use may be associated with weight gain.

DEFINITION

Bipolar disorder (bipolar affective disorder, manic depressive disorder) is characterised by marked mood swings between mania (mood elevation) and bipolar depression that cause significant personal distress or social dysfunction, and are not caused by drugs or known physical disorders. **Bipolar type I disorder** is diagnosed when episodes of depression are interspersed with mania or mixed episodes. **Bipolar type II disorder** is diagnosed when depression is interspersed with less severe episodes of elevated mood that do not lead to dysfunction or disability (hypomania). Bipolar disorder has been subdivided in several further ways (see table 1, p 33). [1]

INCIDENCE/ PREVALENCE

One 1996 cross-national community-based study (38,000 people) found lifetime prevalence rates of bipolar type I disorder ranging from 0.3% in Taiwan to 1.5% in New Zealand. [2] It found that men and women were at similar risk, and that the mean age at first onset ranged from 19–29 years (average of 6 years earlier than first onset of major depression).

AETIOLOGY/ RISK FACTORS

The cause of bipolar disorder is uncertain, although family and twin studies suggest a genetic basis. [3] The lifetime risk of bipolar disorder is increased in first-degree relatives of a person with bipolar disorder (40–70% for a monozygotic twin; 5–10% for other first-degree relatives). If the first episode of mania occurs in an older adult, it may be secondary mania caused by underlying medical or substance-induced factors. [4]

PROGNOSIS

Bipolar disorder is a recurring illness, and one of the leading causes of worldwide disability, especially in the 15–44 years age group. [3] One 4-year inception cohort study (173 people treated for a first episode of mania or mixed affective disorder) found that 93% of people no longer met criteria for mania at 2 years (median time to recover from a syndrome 4.6 weeks), but that only 36% had recovered to premorbid function. [4] It found that 40% of people had a recurrent manic (20%) or depressive (20%) episode within 2 years of recovering from the first episode. A meta-analysis, comparing observed versus expected rates of suicide in an age- and sex-matched sample of the

general population, found that the lifetime prevalence of suicide in people with bipolar disorder was about 2% — or 15 times greater than expected. [5]

AIMS OF INTERVENTION To alleviate mania and bipolar depressive symptoms; to prevent relapse and suicide; to optimise social and occupational functioning; and to improve quality of life, with minimal adverse effects of treatment.

OUTCOMES Level of symptoms on rating scales (completed by clinician, patient, or both); proportion of people with clinically important response to treatment; time to remission; quality of life scores; social and occupational functioning scores; relapse; hospital admission; rates of suicide; frequency of adverse effects; and clinical trial withdrawal rates. Commonly used instruments for assessing symptoms include the Young Mania Rating Scale, which rates 11 manic symptoms with a total score of 0–60; the Schedule for Affective Disorders Change Mania Sub Scale, which rates 18 manic items with a total score of 10–65; and the Hamilton Depression Rating Scale, which has both a 17- and a 21-item version. On these scales, a clinically important response to treatment is usually defined as a greater than 50% reduction in score from baseline. [6] A person is usually considered to be in remission if, at the end of the trial, they score 12 or less on the Young Mania Rating Scale, and 8 or less on the Hamilton Depression Rating Scale. [6] Quality of life is assessed by scales such as the SF-36, and social and occupational functioning on scales such as the Clinical Global Impression Scale.

METHODS *BMJ Clinical Evidence* search and appraisal July 2006. The following databases were used to identify studies for this review: Medline 1966 to July 2006, Embase 1980 to July 2006, Psycinfo 1960 to July 2006, and The Cochrane Database of Systematic Reviews 2006, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE) clinical guidelines. Abstracts of the studies retrieved were assessed independently by two information specialists using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. Some RCTs have been included with less than 80% follow-up, but in whom an intention to treat analysis was undertaken using the last observation carried forward. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded. We also did a search for prospective and retrospective cohort and case series studies on the harms of all interventions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 34).

QUESTION What are the effects of treatments in people with mania associated with bipolar disorder?

OPTION LITHIUM IN MANIA

Symptoms of mania

Compared with placebo Lithium reduces the symptoms of mania compared with placebo after 3–4 weeks (high-quality evidence).

Compared with haloperidol Lithium is as effective as haloperidol at improving the symptoms of mania after 3 weeks (moderate-quality evidence).

Compared with risperidone Lithium is less effective than risperidone at reducing the symptoms of mania after 4 weeks (moderate-quality evidence).

Compared with olanzapine Lithium is as effective as olanzapine at reducing the symptoms of mania after 28 days (moderate-quality evidence).

Compared with valproate Lithium is as effective as valproate at reducing the symptoms of mania after 3–6 weeks (moderate-quality evidence).

Compared with carbamazepine Lithium may be as effective as carbamazepine at reducing the symptoms of mania after 4 weeks (low-quality evidence).

Compared with lamotrigine Lithium may be as effective as lamotrigine at reducing the symptoms of mania after 4 weeks (low-quality evidence).

Lithium plus olanzapine compared with placebo Lithium or valproate plus olanzapine reduces the symptoms of mania compared with placebo after 6 weeks (moderate-quality evidence).

Compared with quetiapine Lithium is as effective as quetiapine at reducing the symptoms of mania after 21 days (moderate-quality evidence).

Compared with topiramate Lithium is more effective than topiramate at reducing the symptoms of mania after 3–12 weeks (moderate-quality evidence).

Remission of mania
Compared with chlorpromazine Lithium may increase the likelihood of remission of mania compared with chlorpromazine after 3 weeks (very low-quality evidence).

Adverse effects
Lithium can cause a range of adverse effects including gastrointestinal disturbances, fine tremor, renal impairment, polydipsia, leucocytosis, weight gain, oedema, and hypothyroidism. It is unclear how these adverse effects compared with those of other antipsychotic drugs.

Note
We found no clinically important results about the effects of lithium compared with clonazepam.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Lithium versus placebo:
We found one systematic review (search date 1999, 1 RCT, 179 people with bipolar type I disorder). [7] The RCT compared three treatments: lithium (36 people), valproate (69 people), and placebo (74 people). It found that lithium significantly increased the proportion of people who responded after 3–4 weeks compared with placebo (response defined as at least 50% improvement in mania score on the Schedule for Affective Disorders and Schizophrenia–Change; 18/36 [50%] with lithium *v* 19/74 [27%] with placebo; RR 1.95, 95% CI 1.17 to 3.23; NNT 5, 95% CI 3 to 20).

Lithium versus placebo or versus quetiapine:
See benefits of quetiapine, p 13 .

Lithium versus chlorpromazine:
We found one systematic review (search date 1999, 4 RCTs, 114 people with bipolar type I disorder). [7] It found that lithium significantly increased the proportion of people who had remission of symptoms at 3 weeks compared with chlorpromazine (remission not defined, 3 RCTs that assessed outcomes at 3 weeks: 23/57 [40%] with lithium *v* 7/57 [12%] with chlorpromazine; RR 1.96, 95% CI 1.02 to 3.77 [figures reported from table 5 in paper]; NNT 4, 95% CI 3 to 9).

Lithium versus haloperidol:
We found one systematic review (search date 1999, 2 RCTs, 50 people with bipolar type I disorder). [7] It found no significant difference between haloperidol and lithium in symptom scores at 3 weeks (assessed by the Brief Psychiatric Rating Scale: effect size –2.14, 95% CI –6.57 to +2.30).

Lithium versus risperidone:
We found one systematic review (search date 1999, 1 RCT, 54 people with bipolar type I disorder). [7] It found that risperidone was significantly more effective than lithium in improving symptom severity score at 4 weeks (assessed by Brief Psychiatric Rating Scale: effect size –2.79, 95% CI –4.22 to –1.36).

Lithium versus olanzapine:
We found no systematic review but found one RCT (30 people with bipolar type I disorder). [8] It found no significant difference between lithium and olanzapine in Young Mania Rating Scale score at 28 days (13.2 with lithium *v* 10.2 with olanzapine; P = 0.315).

Lithium versus valproate:
We found one systematic review (search date 2002, 3 RCTs, 158 people with bipolar type I disorder). [6] It found no significant difference between valproate and lithium in the proportion of people who failed to respond over 3–6 weeks (response defined as 50% reduction in mania score on the Young Mania Rating Scale or the Schedule for Affective Disorders and Schizophrenia–Change; 45/97 [46%] with valproate *v* 26/61 [43%] with lithium; RR 1.05, 95% CI 0.74 to 1.50).

Lithium versus carbamazepine:
We found one systematic review (search date 1999, 3 RCTs, 176 people with bipolar type I disorder). [7] The review could not perform a meta-analysis of all three RCTs because of differences in outcomes assessed. The first RCT (105 people) found no significant difference in the proportion of people who responded over 4 weeks between lithium and carbamazepine (15/54 [28%] with lithium *v* 14/51 [28%] with carbamazepine; RR 1.01, 95% CI 0.54 to 1.88). The other two RCTs (71 people) found no significant difference in global severity of symptoms over 4 weeks between lithium and carbamazepine (assessed by Clinical Global Impression scores: effect size +0.44, 95% CI –0.78 to +1.67). [7]

Lithium versus lamotrigine:
We found no systematic review but found one RCT (30 people with bipolar type I disorder). [9] It found no significant difference between lithium and lamotrigine in Young Mania Rating Scale scores at 4 weeks (mean: 13.2 with lithium *v* 14.3 with lamotrigine; reported as non-significant; no further data reported).

Lithium versus clonazepam:
We found one systematic review (search date 1999), which found two small RCTs (52 people with bipolar type I disorder). [7] However, the RCTs were not of sufficient quality to meet *BMJ Clinical Evidence* inclusion criteria.

Lithium in combination with olanzapine:
See benefits of olanzapine, p 11 .

Lithium versus topiramate:
See benefits of topiramate, p 16 .

Harms:

Lithium has a range of adverse effects, many dose related, including gastrointestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, leucocytosis, weight gain, oedema (may respond to dose reduction), and hypothyroidism.

Lithium versus placebo:
The RCT identified by the review found that lithium significantly increased the proportion of people who had adverse effects compared with placebo (33/36 [92%] with lithium *v* 58/74 [78%] with placebo; RR 1.17, 95% CI 1.00 to 1.37; NNH 8, 95% CI 4 to 334). [7] Adverse effects were not specified.

Lithium versus chlorpromazine:
The review provided inconclusive evidence on the proportion of people who had adverse effects with lithium compared with chlorpromazine. [7] Adverse effects were not specified.

Lithium versus haloperidol:
The review gave no information on adverse effects. [7]

Lithium versus risperidone:
The review gave no information on adverse effects. [7]

Lithium versus olanzapine:
The RCT found no extrapyramidal adverse effects associated with lithium or olanzapine. [8]

Lithium versus valproate:
The review found that valproate significantly reduced the proportion of people who had fever compared with lithium (1 RCT: 1/69 [1%] with valproate *v* 5/36 [14%] with lithium; RR 0.10, 95% CI 0.01 to 0.86). It found no significant difference in the rates of other adverse effects. [6]

Lithium versus carbamazepine:
The review found no significant difference in adverse effects between lithium and carbamazepine (2 RCTs: 27/73 [37%] with lithium *v* 35/66 [53%] with carbamazepine; RR 0.71, 95% CI 0.49 to 1.02). [7] Adverse effects were not specified.

Lithium versus lamotrigine:
The RCT found “no significant adverse effects” between lithium and lamotrigine, but it is likely to have been too small to detect clinically important adverse effects. [9] One person taking lithium withdrew because of a seizure, and one person taking lamotrigine withdrew because of aggravation of diabetes.

Lithium versus clonazepam:
We found no RCTs of sufficient quality.

Lithium in combination with olanzapine:
See harms of olanzapine, p 11 .

Lithium versus placebo or versus quetiapine:
See harms of quetiapine, p 13 .

Lithium versus topiramate:
See harms of topiramate, p 16 .

Comment: None.

OPTION VALPROATE IN MANIA

Symptoms of mania
Compared with placebo Valproate reduces the symptoms of mania compared with placebo after 3 weeks (high-quality evidence).

Compared with lithium Valproate is as effective as lithium at reducing the symptoms of mania after 3–6 weeks (moderate-quality evidence).

Compared with haloperidol Valproate is as effective as haloperidol at reducing the symptoms of mania after 6 days (moderate-quality evidence).

Compared with olanzapine Valproate may be less effective at reducing the symptoms of mania compared with olanzapine after 47 weeks (moderate-quality evidence).

Compared with carbamazepine Valproate is as effective as carbamazepine at reducing the symptoms of mania after 4–6 weeks (moderate-quality evidence).

Valproate or lithium plus olanzapine compared with placebo Valproate or lithium plus olanzapine reduces the symptoms of mania compared with placebo after 6 weeks (moderate-quality evidence).

Compared with quetiapine Valproate may be as effective as quetiapine at reducing the symptoms of mania after 28 days (low-quality evidence).

Adverse effects
Valproate is associated with fewer extrapyramidal adverse effects, and with less sedation compared with haloperidol, but can cause nausea and nervousness.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Valproate versus placebo:
We found one systematic review (search date 2002, 3 RCTs, 316 people with bipolar type I disorder). [6] It found that valproate significantly increased the proportion of people who responded over 3 weeks compared with placebo (response defined as 50% reduction in mania score on the Young Mania Rating Scale [YMRS] or the Schedule for Affective Disorders and Schizophrenia–Change; proportion of people who failed to respond: 66/155 [42%] with valproate *v* 111/161 [69%] with placebo; RR of failing to respond 0.62, 95% CI 0.51 to 0.77). [6]

Valproate versus lithium:
See benefits of lithium, p 3 .

Valproate versus haloperidol:
We found one systematic review (search date 2002, 1 RCT, 36 people with bipolar type I disorder). [6] The RCT found no significant difference in the proportion of people who failed to respond over 6 days between valproate and haloperidol (11/21 [52%] with valproate *v* 10/15 [67%] with lithium; RR 0.79, 95% CI 0.46 to 1.35).

Valproate versus olanzapine:
We found one systematic review (search date 2002, 2 RCTs, 363 people with bipolar type I disorder) and one subsequent RCT. [6] [12] The systematic review found that people taking olanzapine had greater symptom reductions at the end of the trial (unspecified) than those taking valproate (symptoms assessed by the YMRS: WMD 2.81, 95% CI 0.83 to 4.79). One of the RCTs (251 people) found that olanzapine increased the proportion of people who responded at the end of the

trial (unspecified) compared with valproate; however, the difference did not quite reach statistical significance (response defined as 50% reduction in YMRS; proportion of people who failed to respond: 77/123 [63%] with valproate *v* 57/125 [46%] with olanzapine; RR of failing to respond 1.27, 95% CI 0.99 to 1.62). The subsequent double-blind RCT found that olanzapine (5–20 mg/day) significantly improved the YMRS score during the course of the trial and at 47 weeks compared with valproate (500–2500 mg/day) (248 people with manic or mixed episodes; mean difference in YMRS change over course of trial: 2.38, 95% CI 0.89 to 3.87; mean YMRS score at 47 weeks: 15.38 with olanzapine *v* 12.50 with valproate; P = 0.03). [12] It also found that olanzapine significantly reduced median time to remission compared with valproate (remission defined as YMRS 12 or less: 14 days with olanzapine *v* 62 days with valproate; P = 0.05). However, it found no significant difference between treatments in rates of remission over the 47 weeks, or subsequent relapse into mania or depression (AR for remission: 57% with olanzapine *v* 46% with valproate, P = 0.10; AR for relapse, defined as YMRS 15 or more: 42% with olanzapine *v* 56% with valproate, P = 0.42).

Valproate versus carbamazepine:
We found one systematic review (2 RCTs, 59 people with bipolar type I disorder), which found no significant difference between valproate and carbamazepine in the proportion of people who failed to respond at 4–6 weeks (response defined as 50% reduction in mania score on the YMRS or Schedule for Affective Disorders and Schizophrenia–Change: 11/30 [37%] with valproate *v* 16/29 [55%] with carbamazepine; RR 0.66, 95% CI 0.38 to 1.16). [6]

Valproate in combination with olanzapine:
See benefits of olanzapine, p 11 .

Valproate versus quetiapine:
See benefits of quetiapine, p 13 .

Harms:

Valproate versus placebo:
The review found no significant difference between valproate and placebo in the proportion of people who withdrew from the trial because of adverse effects (9/158 [6%] with valproate *v* 5/163 [3%] with placebo; RR 1.95, 95% CI 0.66 to 5.71), but found that people taking valproate were significantly more likely to suffer from dizziness (13/138 [9%] with valproate *v* 4/141 [3%] with placebo; RR 3.17, 95% CI 1.13 to 8.88). [6] No other adverse effects were more commonly reported with valproate than with placebo. We found one small observational study (80 women) which reported that valproate additionally contributed significantly to the development of menstrual abnormalities and an increase in testosterone levels over time when compared with women suffering from bipolar disorder in general. [13] Of 58 women on valproate, 14 (24%) women reported new onset of menstrual abnormalities following treatment with valproate (P = 0.04).

Valproate versus quetiapine:
See harms of quetiapine, p 13 .

Valproate versus lithium:
See harms of lithium, p 3 .

Valproate versus haloperidol:
The RCT found that, compared with haloperidol, valproate caused significantly fewer extrapyramidal adverse effects (0/21 [0%] with valproate *v* 8/15 [53%] with haloperidol; RR 0.04, 95% CI 0 to 0.69), dry mouth (1/21 [5%] with valproate *v* 3/15 [20%] with haloperidol; RR 0.24, 95% CI 0.03 to 2.07), and was less likely to cause sedation than haloperidol (1/21 [5%] with valproate *v* 4/15 [27%] with haloperidol; RR 0.18, 95% CI 0.02 to 1.44). [6]

Valproate versus olanzapine:
The review found no significant difference between valproate and olanzapine in the proportion of people who withdrew because of adverse effects (1 RCT: 9/126 [7%] with valproate *v* 12/125 [10%] with olanzapine; RR 0.74, 95% CI 0.33 to 1.70) or had movement disorders (akathisia: WMD –0.02, 95% CI –0.27 to +0.23; abnormal involuntary movement [using Abnormal Involuntary Movement Scale]: WMD –0.17, 95% CI –0.62 to +0.28). [6] It found that valproate caused significantly more nausea than olanzapine (1 RCT: 36/126 [29%] with valproate *v* 13/125 [10%] with olanzapine; RR 2.75, 95% CI 1.53 to 4.93), but caused less increased appetite (1 RCT: 3/126 [2%] with valproate *v* 15/125 [12%] with olanzapine; RR 0.20, 95% CI 0.06 to 0.67), less weight gain (WMD –2.14 kg, 95% CI –2.65 kg to –1.62 kg), less dry mouth (8/126 [6%] with valproate *v* 42/125 [34%] with olanzapine; RR 0.19, 95% CI 0.09 to 0.39), and less sedation (2 RCTs: 44/189 [23%] with valproate *v* 76/182 [42%] with olanzapine; RR 0.55, 95% CI 0.41 to 0.76). The subsequent RCT found that olanzapine significantly increased somnolence (46% with olanzapine *v* 25% with valproate; P < 0.001), dry mouth (34% with olanzapine *v* 7% with valproate; P < 0.001), increased appetite

(14% with olanzapine *v* 6% with valproate; P = 0.04), weight gain (25% with olanzapine *v* 12% with valproate; P = 0.01), and akathisia (10% with olanzapine *v* 2% with valproate; P = 0.006) compared with valproate. [12] It found that valproate significantly increased nausea (32% with valproate *v* 16% with olanzapine; P = 0.005) and nervousness (22% with valproate *v* 12% with olanzapine; P = 0.05) compared with olanzapine.

Valproate versus carbamazepine:
One RCT (28 people identified by the review) assessed adverse effects. [6] It found no significant difference in adverse effects between valproate and carbamazepine, but it is likely to have been underpowered to detect a clinically important difference.

Valproate in combination with olanzapine:
See harms of olanzapine, p 11 .

Comment: **Clinical guide:**
There are several formulations of valproic acid available, including sodium valproate, valpromide, and valproate semisodium (divalproex). Valproate semisodium is the only preparation licensed for treatment of mania in the UK. In this review, we refer to the generic as valproate because this is the term in common usage.

OPTION CHLORPROMAZINE IN MANIA

Symptoms of mania
Compared with placebo Chlorpromazine may be more effective than placebo at reducing the symptoms of mania after 7 weeks (low-quality evidence).

Compared with imipramine Chlorpromazine may be more effective than imipramine at reducing the effects of mania after 7 weeks (low-quality evidence).

Remission of mania
Compared with chlorpromazine Chlorpromazine may be less likely than lithium to induce remission of mania after 3 weeks (very low-quality evidence).

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: **Chlorpromazine versus placebo:**
We found one non-systematic review, which identified one small RCT (13 people with mania) comparing three treatments: chlorpromazine, imipramine, and placebo. [15] It found that chlorpromazine significantly improved global outcome at 7 weeks compared with imipramine or placebo (assessed on a scale from –9 to +9, where +9 = improvement: +6.1 with chlorpromazine *v* +2.0 with imipramine *v* –2.8 with placebo; reported as significant; no further data reported).

Chlorpromazine versus lithium:
See benefits of lithium, p 3 .

Harms: **Chlorpromazine versus placebo:**
The non-systematic review gave no information on adverse effects. [15]

Chlorpromazine versus lithium:
See harms of lithium, p 3 .

Comment: **Clinical guide:**
The evidence for older antipsychotic drugs is sparse, and there are currently no systematic reviews available. The drugs are, however, widely used in mania.

OPTION HALOPERIDOL IN MANIA

Symptoms of mania
Compared with placebo Haloperidol reduces the symptoms of mania compared with placebo after 21 days (moderate-quality evidence).

Compared with quetiapine Haloperidol may be as effective as quetiapine at reducing symptoms of mania after 21 days (low-quality evidence).

Compared with risperidone Haloperidol is as effective as risperidone at reducing the symptoms of mania (moderate-quality evidence).

Compared with lithium Haloperidol is as effective as lithium at improving the symptoms of mania after 3 weeks (moderate-quality evidence).

Compared with valproate Haloperidol is as effective as valproate at reducing the symptoms of mania after 6 days (moderate-quality evidence).

Compared with olanzapine Haloperidol is as effective as olanzapine at reducing the symptoms of mania after 6 weeks (high-quality evidence).

Relapse of mania
Compared with olanzapine Haloperidol is as effective as olanzapine at preventing relapse of mania after 6 weeks (high-quality evidence).

Adverse effects
Haloperidol has been associated with a higher rate of extrapyramidal adverse effects and sedation compared with valproate.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Haloperidol versus placebo or versus quetiapine:
We found one three-limbed RCT (302 people, bipolar 1 disorder with manic episode) which compared 12 weeks treatment with quetiapine (flexibly dosed up to 800 mg/day), placebo, or haloperidol (up to 8 mg/day). [16] It found that Young Mania Rating Scale score significantly improved with quetiapine compared with placebo at day 21 (–12.29 with quetiapine *v* –8.32 with placebo; P < 0.01). It found that haloperidol significantly improved Young Mania Rating Scale score compared with placebo at day 21 (–15.71 with haloperidol *v* –8.32 with placebo; P < 0.001). A *post hoc* analysis found that there was no significant difference in efficacy measures between quetiapine and haloperidol groups at any assessment except day 21 (P < 0.05 in favour of haloperidol). However, the RCT reported that the study was prospectively powered to detect differences between haloperidol or quetiapine versus placebo, but not differences between quetiapine and haloperidol. [16] Although the RCT analysed by intention to treat, the numbers of people completing at day 21 were 66/102 (65%) with quetiapine, 61/101 (60%) with placebo, and 77/99 (78%) with haloperidol, with the analysis using the last observation carried forward. The high withdrawal rate may limit the generalisability of the results.

Haloperidol versus risperidone:
See benefits of risperidone, p 10 .

Haloperidol versus lithium:
See benefits of lithium, p 3 .

Haloperidol versus valproate:
See benefits of valproate, p 6 .

Haloperidol versus olanzapine:
We found one double-blind RCT comparing haloperidol (3–15 mg) versus olanzapine (5–20 mg). [17] It found no significant difference between treatments in remission or relapse at 6 weeks or time to remission (219 people; remission defined as Young Mania Rating Scale < 12, AR: 46% with haloperidol *v* 52% olanzapine, P = 0.15; relapse defined as Young Mania Rating Scale score > 15, AR: 14.8% with haloperidol *v* 13.1% with olanzapine, P = 0.56; median time to remission: 29 days with haloperidol *v* 34 days with olanzapine, P = 0.98. There was no significant difference in the proportion of people receiving benzodiazepines at least once (60% with olanzapine *v* 65% with haloperidol, P = 0.33).

Harms:

Haloperidol versus placebo:
We found no RCTs.

Haloperidol versus placebo or versus quetiapine:
The RCT reported that the only common adverse effect with quetiapine was somnolence (13/102 [13%] people), and that no adverse effects in the quetiapine group occurred significantly more than in the placebo group. [16] The RCT reported that, compared with placebo, haloperidol significantly increased tremor (30% with haloperidol *v* 6% with placebo; P < 0.001), akathisia (33% *v* 6%; P < 0.001), and extrapyramidal symptoms (35% *v* 6%; P < 0.001). [16]

Haloperidol versus risperidone:
See harms of risperidone, p 10 .

Haloperidol versus lithium:
See harms of lithium, p 3 .

Haloperidol versus valproate:
See harms of valproate, p 6 .

Haloperidol versus olanzapine:
The RCT found no significant difference between haloperidol and olanzapine in withdrawals caused by adverse effects (11% with haloperidol *v* 8% with olanzapine; P = 0.27). [17] It found that haloperidol significantly increased extrapyramidal adverse effects compared with olanzapine (akathisia: 30% with haloperidol *v* 6% with olanzapine, P < 0.001; extrapyramidal syndrome: 24% with haloperidol *v* 2% with olanzapine, P < 0.001). Olanzapine significantly increased somnolence and weight gain compared with haloperidol (somnolence: 15% with olanzapine *v* 9% with haloperidol, P = 0.04; weight gain: 14% with olanzapine *v* 4% with haloperidol, P < 0.001).
Drug safety alert:
Since the last update of this review, a drug safety alert has been issued on cardiovascular side-effects and sudden death associated with haloperidol (www.fda.gov/cder/drug/InfoSheets/HCP/haloperidol.htm).

Comment:

Clinical guide:
The evidence for older antipsychotics is sparse, and there are currently no systematic reviews available. The drugs are, however, widely used in mania.

OPTION RISPERIDONE IN MANIA

Symptoms of mania
Compared with placebo Risperidone reduces the symptoms of mania compared with placebo (high-quality evidence).

Compared with lithium Risperidone is more effective than lithium at reducing the symptoms of mania after 4 weeks (moderate-quality evidence).

Compared with haloperidol Risperidone is as effective as haloperidol at reducing the symptoms of mania (moderate-quality evidence).

Compared with placebo as an adjunct to lithium, valproate or carbamazepine Risperidone is more effective than placebo at reducing the symptoms of mania in people taking lithium, valproate or carbamazepine (high-quality evidence).

Adverse effects
Risperidone has been associated with somnolenceand extrapyramidal adverse effects.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Risperidone versus placebo:
We found one systematic review, [18] one subsequent report of an RCT included in the review, [19] and one subsequent RCT. [20] The review (search date 2004, people with acute mania) found that risperidone was significantly more effective than placebo in improving the Young Mania Rating Scale score (mean change in Young Mania Rating Scale [YMRS] score: 2 RCTs, 537 people; WMD –5.75, 95% CI –7.46 to –4.04; P < 0.00001). [18] One RCT included in the review [18] as an abstract was subsequently published in full. [19] This RCT (291 people with mania) compared flexible doses of risperidone (1–6 mg/day) versus placebo for up to 3 weeks. [19] Remission was defined as achieving and maintaining a YMRS score 8 or less for the remainder of the trial or until censor. It found that remission was achieved by 61/146 (42%) of people receiving risperidone compared with 18/144 (13%) of people receiving placebo. After adjusting for psychosis, baseline YMRS score, sex, number of mood cycles in the previous year, and treatment, it found that the odds of remission for people receiving risperidone were significantly higher than those for placebo (logistic regression analysis: OR 5.6, 95% CI 3.0 to 10.4; P < 0.0001). [19] The subsequent 3-week RCT included 290 current manic or mixed episode people with a score of 20 or more on YMRS. [20] Risperidone (1–6 mg/day) was allocated to 146 people and placebo to 144 people. It found that significantly greater improvements were observed with risperidone than with placebo at weeks 1 and 2 and at the end point (total YMRS: P < 0.01). [20]

Risperidone versus lithium:
See benefits of lithium, p 3 .

Risperidone versus haloperidol:
We found one systematic review. [18] The review (search date 2004, people with acute mania) found no evidence for a significant difference between risperidone and haloperidol in mean change measured by the YMRS score (1 RCT, 297 people, WMD –1.20, 95% CI –3.54 to + 1.14; P = 0.32). [18]

Risperidone added to lithium, valproate, or carbamazepine:
See benefits of lithium, p 3 . See also benefits of valproate, p 6 . We found one systematic review. [18] The review (search date 2004, people with acute mania) found that risperidone was significantly more effective than placebo as adjunctive treatment to lithium or an anticonvulsant, measured as mean change on the YMRS compared with placebo (2 RCTs, 238 people, WMD –5.16, 95% CI –7.99 to –2.32; P = 0.0004). [18]

Harms:

Risperidone versus placebo:
The most common adverse effect reported among risperidone patients was somnolence. The review found a significant increase in sedation with risperidone compared with placebo (3 RCTs, 843 people, RR 3.39, 95% CI 1.96 to 5.86; P < 0.0001). [18] It also found a greater increase in extrapyramidal symptoms measured on the Extrapyramidal Symptom Rating Scale compared with placebo (1 RCT, 247 people, WMD 0.6, 95% CI 0.00 to 1.20; P = 0.05). [18] Although Extrapyramidal Symptom Rating Scale scores were significantly greater in people receiving risperidone, mean total and subscale scores were low. [21] The subsequent RCT found that extrapyramidal symptoms were the most frequently reported adverse effects in the risperidone group (35% in the risperidone group *v* 6% with placebo; between group significance not reported). [20]

Risperidone versus lithium:
See harms of lithium, p 3 .

Risperidone versus haloperidol:
The review found no significant difference between risperidone and haloperidol as adjunctive treatment to lithium or an anticonvulsant, in terms of the number of people who experienced one or more adverse effects (1 RCT, 105 people, RR 0.87, 95% CI 0.75 to 1.02; P = 0.08). [18] One included RCT found that extrapyramidal disorders and hyperkinesias, the most commonly reported adverse effects with antipsychotic use, occurred less frequently with risperidone than with haloperidol. [22]

Risperidone added to lithium, valproate, or carbamazepine:
See harms of lithium, p 3 . See also harms of valproate, p 20 . The review found no significant difference between risperidone and placebo as adjunctive treatment to lithium or an anticonvulsant in terms of the proportion of people who experienced one or more adverse effects (2 RCTs, 253 people, RR 1.04, 95% CI 0.88 to 1.23; P = 0.66). [18]

Comment:

The systematic review noted high withdrawal rates in some of the included RCTs with an intention-to-treat analysis being performed by the RCTs using the last observation carried forward. [18] It noted that the high withdrawal rates may limit confidence in the results. [18]

OPTION OLANZAPINE IN MANIA

Symptoms of mania
Compared with placebo Olanzapine reduces the symptoms of mania compared with placebo after a single injection, or after 3–4 weeks of continuous therapy (moderate-quality evidence).

Compared with lithium Olanzapine is as effective as lithium at reducing the symptoms of mania after 28 days (moderate-quality evidence).

Compared with valproate Olanzapine may be less effective at reducing the symptoms of mania compared with valproate after 47 weeks (moderate-quality evidence).

Compared with haloperidol Olanzapine is as effective as haloperidol at reducing the symptoms of mania after 6 weeks (high-quality evidence).

Olanzapine plus valproate or lithium compared with placebo Olanzapine plus valproate or lithium reduces the symptoms of mania compared with placebo after 6 weeks (moderate-quality evidence).

Adverse effects
Olanzapine has been associated with adverse effects including weight gain, somnolence, dry mouth, weakness, and dizziness.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Olanzapine versus placebo:
We found one systematic review [23] and one subsequent RCT. [24] The review (search date 2002, 6 RCTs, 1422 people with bipolar type I disorder) found that olanzapine significantly increased the proportion of people who responded over 3–4 weeks compared with placebo (response defined as 50% reduction in mania score on the Young Mania Rating Scale; 2 RCTs; proportion who failed to respond: 56/125 [45%] with olanzapine *v* 89/129 [69%] with placebo; RR of failing to respond: 0.64, 95% CI 0.52 to 0.81). [23] The subsequent RCT (201 people with bipolar type I disorder and agitation) compared 1–3 intramuscular injections of olanzapine (10 mg/10 mg/5 mg), lorazepam (2 mg/2 mg/1 mg), and placebo. [24] It found that olanzapine significantly increased the proportion of people who responded at 2 hours after the first injection compared with placebo (response defined as a 40% or greater reduction in the Positive and Negative Syndrome Scale, Excited Component: at 2 hours: 81% with olanzapine *v* 44% with placebo; RR 1.85, 95% CI 1.40 to 2.67; NNT 3, 95% CI 2 to 4. The difference was not significant at 24 hours.

Olanzapine in combination with lithium or valproate:
The systematic review found that olanzapine plus lithium or valproate significantly increased the proportion of people who responded at 6 weeks compared with placebo (search date 2002, 1 RCT; proportion who failed to respond: 80/229 [35%] with olanzapine *v* 64/115 [56%] with placebo; RR of failing to respond: 0.63, 95% CI 0.49 to 0.80). [23]

Olanzapine versus lithium:
See benefits of lithium, p 3 .

Olanzapine versus valproate:
See benefits of valproate, p 6 .

Olanzapine versus haloperidol:
See benefits of haloperidol, p 8 .

Harms:

The review found that olanzapine, both as monotherapy and in combination with lithium or valproate, caused significantly more weight gain than placebo (3 RCTs, 581 people: WMD 2.27 kg, 95% CI 1.56 kg to 2.99 kg). [23] It found no significant difference in movement disorders between olanzapine and placebo (measured on the Barnes Akathisia Scale; 2 RCTs, 246 people: WMD –0.13, 95% CI –0.32 to + 0.06), but found that olanzapine significantly increased somnolence (162/354 [46%] with olanzapine *v* 48/244 [20%] with placebo; RR 2.13, 95% CI 1.62 to 2.79), dry mouth (100/354 [28%] with olanzapine *v* 18/244 [7%] with placebo; RR 3.64, 95% CI 2.24 to 5.91), dizziness (54/354 [15%] with olanzapine *v* 16/244 [7%] with placebo; RR 2.37, 95% CI 1.39 to 4.04), muscle weakness (61/354 [17%] with olanzapine *v* 23/244 [9%] with placebo; RR 1.69, 95% CI 1.09 to 2.64), increased appetite (54/229 [24%] with olanzapine *v* 9/115 [8%] with placebo; RR 3.01, 95% CI 1.54 to 5.88), and speech disorder (15/229 [7%] with olanzapine *v* 1/115 [1%] with placebo; RR 7.53, 95% CI 1.01 to 56.32).

Olanzapine versus lithium:
See harms of lithium, p 3 .

Olanzapine versus valproate:
See harms of valproate, p 6 .

Olanzapine versus haloperidol:
See harms of haloperidol, p 8 .

Comment:

None.

OPTION ZIPRASIDONE IN MANIA

Symptoms of mania
Compared with placebo Ziprasidone reduces the symptoms of mania compared with placebo after 3 weeks (moderate-quality evidence).

Adverse effects
Ziprasidone has been associated with somnolence, dizziness, and extrapyramidal symptoms.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Ziprasidone versus placebo:
We found one two RCTs. [25] [26] The first RCT (201 people aged 18 years or more with bipolar type I disorder) compared ziprasidone 80–160 mg daily versus placebo for 3 weeks. [25] It found that ziprasidone significantly increased the proportion of people who responded at 3 weeks compared with placebo (response defined as a 50% or more reduction in Young Mania Rating Scale score from baseline: 50% with ziprasidone *v* 35% with placebo; RR 1.45, 95% CI 1.02 to 2.13; NNT 6, 95% CI 3 to 128). The second RCT (202 people with bipolar type I disorder with manic or mixed episode with Mania Rating Scale score 14 or more) randomised people to ziprasidone (40–80 mg twice daily; 139 people) or placebo (66 people). [26] The main outcome measure was change in the Mania Rating Scale score at 3 weeks. [26] The RCT found that ziprasidone significantly improved symptoms compared with placebo (change from baseline in mean Mania Rating Scale score: –11.1 with ziprasidone *v* –5.6 with placebo; P < 0.01). [26] Although the RCT used an intention-to-treat analysis, discontinuation rates were high (55/140 [39%] with ziprasidone *v* 30/66 [45%] with placebo) and the analysis used the last observation carried forward. [26] The high withdrawal rates may limit the generalisability of the results.

Harms:

Ziprasidone versus placebo:
The RCT found that, compared with placebo, more people taking ziprasidone had somnolence (37% with ziprasidone *v* 13% with placebo), dizziness (22% with ziprasidone *v* 10% with placebo), and akathisia (11% with ziprasidone *v* 6% with placebo; CI not reported for any outcome). [25] The RCT reported that treatment-related discontinuations caused by adverse effects were 5.8% of people for ziprasidone and 1.5% of people for placebo (P = 0.20). [26] It found that, compared with placebo, ziprasidone significantly increased somnolence (22% with ziprasidone *v* 6% with placebo; P = 0.002), extrapyramidal syndrome (11% *v* 1.5%; P = 0.013), and dizziness (10% *v* 1.5%; P = 0.018). [26]

Comment: None.

OPTION QUETIAPINE IN MANIA

Symptoms of mania
Compared with placebo Quetiapine reduces the symptoms of mania compared with placebo after 21 days (moderate-quality evidence).

Compared with placebo as adjunct treatment Quetiapine reduces the symptoms of mania compared with placebo in people taking valproate after 6 weeks (moderate-quality evidence).

Compared with lithium Quetiapine is as effective as lithium at reducing the symptoms of mania after 21 days (moderate-quality evidence).

Compared with haloperidol Quetiapine may be as effective as haloperidol at reducing symptoms of mania after 21 days (low-quality evidence).

Compared with valproate Quetiapine may be as effective as valproate at reducing the symptoms of mania after 28 days (low-quality evidence).

Adverse effects
Quetiapine has been associated with dry mouth, somnolence, and weight gain.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Quetiapine versus placebo as an add on to valproate:
We found one RCT (30 inpatients aged 12–18 years with bipolar type I disorder) comparing quetiapine up to 450 mg daily as an adjunctive treatment to valproate (divalproex) versus placebo plus valproate for 6 weeks. [27] It found that quetiapine significantly increased the proportion of people who responded at 6 weeks compared with placebo (response defined as 50% or more reduction in score on the Young Mania Rating Scale (YMRS): 87% with quetiapine *v* 53% with placebo; RR 1.63, 95% CI 1.01 to 2.94).

Quetiapine versus placebo or versus lithium:
We found one double-blind RCT (302 people with mania) which compared quetiapine (flexibly dosed up to 800 mg/day), placebo, and lithium. [10] More people in the quetiapine (97/107 [91%]) and lithium (84/98 [85%]) groups completed the study at day 21 compared with the placebo group (67/97 [69%]). It found that the reduction in YMRS score was significantly greater for quetiapine compared with placebo at day 7 (–8.03 with quetiapine *v* –4.89 with placebo; P < 0.01) and day 21 (–14.6 *v* –6.7; P < 0.001). It found that, compared with placebo, significantly more people with quetiapine fulfilled YMRS response criteria at day 21 (53% with quetiapine *v* 27% with placebo;

P < 0.001). It found that lithium-treated patients improved significantly compared with placebo-treated patients at day 21 (–15.2 with lithium *v* –6.7 with placebo; P < 0.001). [10] It found no significant difference between quetiapine and lithium in YMRS score at 21 days (P value not reported). However, the RCT reported that it was prospectively powered to detect differences between quetiapine versus placebo, but not differences between quetiapine and lithium.

Quetiapine versus placebo or versus haloperidol:
See benefits of haloperidol, p 8 .

Quetiapine versus valproate:
We found one small RCT (50 adolescents with bipolar type I disorder, manic or mixed episode, YMRS score 20 or more at baseline), which compared quetiapine (400–600 mg/day) versus valproate (divalproex) (serum level 80–120 microg/mL) for 28 days. [14] The RCT found no significant difference between quetiapine and valproate in YMRS score at 28 days (between-group difference in change of YMRS score from baseline: 3.3, 95% CI –3.5 to +10.1). [14] It reported that YMRS scores improved more rapidly with quetiapine than with valproate (regression analysis: P = 0.01). [14] In total, 38/50 (76%) completed the trial, and the analysis was by intention to treat using the last observation carried forward. This may limit the generalisability of the results.

Harms:

Quetiapine versus placebo:
We found no RCTs.

Quetiapine versus placebo as an add-on to valproate:
The RCT found that quetiapine significantly increased the proportion of adolescents who experienced sedation compared with placebo (12/15 [80%] with quetiapine *v* 5/15 [33%] with placebo; P = 0.03). [27]

Quetiapine versus placebo or versus lithium:
The most common adverse effects for quetiapine were dry mouth (24% with quetiapine *v* 2% with placebo *v* 6% with lithium), somnolence (20% *v* 3% *v* 9%), and weight gain (15% *v* 1% *v* 6%), whereas lithium was associated with tremor (6% *v* 4% *v* 18%) and insomnia (10% *v* 20% *v* 16%; between-group P values not reported). [10] The quetiapine and placebo groups had similar, low levels of extrapyramidal symptom-related adverse effects. [10]

Quetiapine versus placebo or versus haloperidol:
See harms of haloperidol, p 20 .

Quetiapine versus valproate:
The RCT reported that rates of adverse effects did not differ significantly between groups. [14]

Comment: None.

OPTION CARBAMAZEPINE IN MANIA

Symptoms of mania
Compared with placebo Carbamazepine reduces the symptoms of mania compared with placebo after 21 days (moderate-quality evidence).

Compared with lithium Carbamazepine may be as effective as lithium at reducing the symptoms of mania after 4 weeks (low-quality evidence).

Compared with valproate Carbamazepine is as effective as valproate at reducing the symptoms of mania after 4–6 weeks (moderate-quality evidence).

Adverse effects
Carbamazepine is associated with dizziness, nausea, and somnolence.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Carbamazepine versus placebo:
We found no systematic review, but found two double-blind RCTs. [28] [29] The first RCT found that extended-release carbamazepine (400–1600 mg/day) significantly increased the response rate at 21 days compared with placebo (204 people with *Diagnostic and Statistical Manual of Mental Disorders* IV [DSM-IV]-defined manic or mixed episodes, 192 people in a last observation carried forward analysis; response defined as a 50% decrease in Young Mania Rating Scale; AR: 42% with carbamazepine *v* 22% with placebo; RR 1.86, 95% CI 1.23 to 2.87; NNT 5, 95% CI 3 to 15). [28] The second RCT (239 people with manic or mixed episodes) used a similar protocol and

the same interventions as the first RCT. [29] It found that extended-release carbamazepine significantly reduced YMRS total scores compared with placebo at 21 days (change in YMRS total scores from baseline to day 21: 28.46 to 13.38 with carbamazepine *v* 27.3 to 20.82 with placebo; P < 0.001). [29] In total, 144/239 (60%) completed the trial. Analysis was by intention to treat with the last observation carried forward to the analysis.

Carbamazepine versus lithium:
See benefits of lithium, p 3 .

Carbamazepine versus valproate:
See benefits of valproate, p 6 .

Harms:

Carbamazepine versus placebo:
The first RCT found that carbamazepine increased withdrawals caused by adverse effects, but the increase was not statistically significant (13% with carbamazepine *v* 6% with placebo; P = 0.09). [28] It found that carbamazepine increased dizziness, nausea, and somnolence compared with placebo, but the significance of these differences was not reported (dizziness: 49% with carbamazepine *v* 13% with placebo; nausea: 38% with carbamazepine *v* 11% with placebo; somnolence: 33% with carbamazepine *v* 16% with placebo; significance assessments not performed). No person gained more than 7% of body weight with either treatment. The second RCT found that carbamazepine significantly increased the proportion of people with adverse effects compared with placebo (91% with carbamazepine *v* 56% with placebo; P < 0.0001). [29] The most common adverse effects were dizziness (41% with carbamazepine *v* 12% with placebo; P < 0.001), somnolence (27% *v* 10%; P = 0.001), nausea (23% *v* 9%; P = 0.0032), ataxia (19% *v* 0%; P < 0.0001), and vomiting (16% *v* 3%; P = 0.0003). [29]

Carbamazepine versus lithium:
See harms of lithium, p 3 .

Carbamazepine versus valproate:
See harms of valproate, p 6 .

Comment: None.

OPTION CLONAZEPAM IN MANIA

Symptoms of mania
Compared with placebo Clonazepam may reduce the symptoms of mania compared with placebo after 5 days (low-quality evidence).

Adverse effects
Clonazepam has been associate with tremor, blurred vision, and somnolence.

Note
We found no clinically important results about the effects of clonazepam compared with lithium.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Clonazepam versus placebo:
We found one systematic review (search date 2000), [30] which identified one small RCT. [31] The RCT used a 10-point clinical global rating scale to assess manic and psychotic symptoms (score range 0–9; higher score indicating more severe symptoms). It found that clonazepam (6 mg/day) significantly reduced manic but not psychotic symptoms at 5 days compared with placebo (30 people; median reduction in manic rating score: 3.25 with clonazepam *v* 2.25 with placebo, P < 0.05; median reduction in psychotic scale score: 0.60 with clonazepam *v* 0.086 with placebo, difference reported as not significant, figures not reported).

Clonazepam versus lithium:
See benefits of lithium, p 3 .

Harms:

Clonazepam versus placebo:
The small RCT identified by the systematic review [30] assessed adverse effects using a 9-point nurse- and participant-rated global score (higher score indicating greater severity). [31] It found that clonazepam significantly increased overall adverse effects, tremor, blurred vision, and sleepiness compared with placebo (median scores for overall adverse effects: 4.4 with clonazepam *v* 1.9 with placebo, P < 0.001; tremor: 1.0 with clonazepam *v* 0.0 with placebo, P < 0.05; blurred vision: 2.5

with clonazepam *v* 0.0 with placebo, P < 0.05; sleepiness: 4.0 with clonazepam *v* 1.0 with placebo, P < 0.01). [31]

Clonazepam versus lithium:
See harms of lithium, p 3 .

Comment: None.

OPTION GABAPENTIN IN MANIA

Symptoms of mania
Compared with placebo Gabapentin may be worse than placebo at reducing the symptoms of mania in people also taking valproate or lithium (moderate-quality evidence).

Adverse effects
Gabapentin has been associated with somnolence, dizziness, diarrhoea, and memory loss.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: **Gabapentin versus placebo:**
We found one double-blind RCT (117 people aged > 16 years with bipolar type I disorder, all taking either valproate or lithium) comparing gabapentin 600–3600 mg daily versus placebo over 10 weeks. [32] It found that gabapentin reduced symptoms significantly less than placebo on the Young Mania Rating Scale (mean reduction: –6.5 with gabapentin *v* –9.9 with placebo; mean difference 3.34, 95% CI 0.32 to 6.35; P = 0.03).

Harms: **Gabapentin versus placebo:**
The RCT found that, compared with placebo, more people taking gabapentin had somnolence (24% with gabapentin *v* 12% with placebo), dizziness (19% with gabapentin *v* 5% with placebo), diarrhoea (16% with gabapentin *v* 12% with placebo), and memory loss (10% with gabapentin *v* 3% with placebo; CI not reported for any outcome). [32]

Comment: None.

OPTION LAMOTRIGINE IN MANIA

Symptoms of mania
Compared with lithium Lamotrigine may be as effective as lithium at reducing the symptoms of mania after 4 weeks (low-quality evidence).

Adverse effects
Lamotrigine may have similar adverse effects to lithium.

Note
We found no direct information about whether or not lamotrigine is better than no active treatment in people with mania.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: **Lamotrigine versus placebo:**
We found no systematic review or RCTs.

Lamotrigine versus lithium:
See benefits of lithium, p 3 .

Harms: **Lamotrigine versus placebo:**
We found no RCTs.

Lamotrigine versus lithium:
See harms of lithium, p 3 .

Comment: None.

OPTION TOPIRAMATE IN MANIA

Symptoms of mania

Compared with placebo Topiramate is no better than placebo at reducing the symptoms of mania after 3–12 weeks (moderate-quality evidence).

Compared with lithium Topiramate is less effective than lithium at reducing the symptoms of mania after 3–12 weeks (moderate-quality evidence).

Adverse effects
Topiramate has been associated with adverse effects including weight loss, somnolence, dizziness, headache, confusion, and visual problems.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Topiramate versus placebo:
We found one systematic review (search date 2001), which identified one double-blind RCT. [33] The RCT found no significant difference between topiramate (256 and 512 mg/day) and placebo in symptoms at 3 weeks (97 people with mania; Young Mania Rating Scale (YMRS) total score: 19.6 with 512 mg topiramate *v* 21.1 with 256 mg topiramate *v* 23.7 with placebo; difference reported as not significant, P value and CI not reported). We found one subsequent report of four double-blind RCTs with similar methods, which compared 659 people with bipolar type I disorder and acute mania taking topiramate (200–600 mg/day) with 429 people taking placebo, which pooled data. [11] The core study duration in all RCTs was 3 weeks; three trials also had 9-week double-blind extensions. The primary outcome measure was mean YMRS change over 3 weeks. The study found no significant difference between topiramate and placebo in YMRS scores (mean YMRS reductions in the 4 RCTs: range 5.1 to 8.2 with topiramate *v* range 6.4 to 8.4 with placebo; reported as non significant, P value not provided). The study reported that a similar pattern was observed after 12 weeks of double-blind treatment in studies with double-blind extensions. [11]

Topiramate versus lithium:
We found one report of two double-blind RCTs comparing 336 people taking topiramate (200–400 mg/day) with 227 people taking lithium (1500 mg/day) which pooled data (see topiramate versus placebo section above). [11] The report found that improvement in YMRS scores with lithium were significantly greater than those with topiramate (absolute figures in analysis not reported; $P < 0.001$). [11] The study reported that a similar pattern was observed after 12 weeks of double-blind treatment in studies with double-blind extensions.

Harms:

Topiramate versus placebo:
We found three systematic reviews (search dates 2001 and 2003) in people with mood disorders. [33] [34] [35] The first systematic review gave no information on adverse effects. [33] The second systematic review found no RCTs, but data from identified observational studies suggested that topiramate may lead to weight reduction in people with mood disorders (3 cohort studies; weight loss at 1 year [56 people]: 0.7–6.2 kg; weight loss at 4 weeks [14 people]: 1–8 kg; mean weight loss at 10 weeks [15 people]: 4.2 kg). [35] One large retrospective study identified by the review (214 people) found that, over 3 months, 65% of people taking topiramate lost weight. The third review (search date 2001) of topiramate identified no RCTs in people with bipolar disorder. [34] It found that, in people with epilepsy, the most common adverse effects associated with topiramate were fatigue, dizziness, headache, abnormal thinking, confusion, somnolence, ataxia, impaired concentration, nystagmus, double vision, and anorexia. The subsequent study found that paraesthesia, appetite decrease, dry mouth, and weight loss were more frequently (3% higher incidence rate or more) associated with topiramate than with placebo (between-group P values not reported). [11] The incidence of serious effects was 2% with placebo and 2–7% with topiramate (between-group P values not reported).

Comment: None.

QUESTION What are the effects of treatments in bipolar depression?

OPTION PSYCHOLOGICAL TREATMENTS IN BIPOLAR DEPRESSION

We found no clinically important results about the effects of psychological treatments in people with bipolar depression.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found no systematic review or RCTs in people with bipolar depression (see comment below).

Harms: We found no RCTs.

Comment: We found no RCTs of psychological interventions in bipolar depression. It is unclear if it is reasonable to extrapolate from the evidence for treatments for unipolar depression.

Clinical guide:
It is likely that specific psychological interventions will have some effect, but RCTs are needed to estimate the size of any benefits and harms of these treatments (see review on depression in adults: drug and physical treatments).

OPTION ANTIDEPRESSANTS IN BIPOLAR DEPRESSION

Symptoms of depression
Compared with placebo Antidepressants (fluoxetine, paroxetine, imipramine, tranylcypromine, and deprenyl) reduce the symptoms of depression compared with placebo after 4–10 weeks (high-quality evidence).

Tricyclic antidepressants compared with selective serotonin reuptake inhibitors Tricyclic antidepressants may be less likely to lead to clinical response after 4–10 weeks comapred with selective serotonin reuptake inhibitors (moderate-quality evidence).

Adding antidepressants compared with adding second dose of lithium or valproate Adding antidepressants (paroxetine) to lithium or valproate may be as effective as adding a second dose of lithium or valproate after 6 weeks (low-quality evidence).

Moclobemide compared with imipramine Moclobemide may be as effective as imipramine at reducing symptoms of depression (low-quality evidence).

Manic switching
Antidepressants compared with placebo Antidepressants have been associated with manic switching, but the increase in risk may be low compared with placebo (high-quality evidence).

Tricyclic antidepressants compared with selective serotonin reuptake inhibitors Tricyclic antidepressants may be more likely than selective serotonin reuptake inhibitors to induce mania (moderate-quality evidence).

Other adverse effects
SSRIs have been linked to suicidal ideation, persistent pulmonary hypertension in infants born to women who had taken SSRIs during the latter half of pregnancy, congenital malformations in infants born to women taking paroxetine during the first trimester of pregnancy, and hyponatraemia.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Antidepressants versus placebo:
We found one systematic review. [36] It found that antidepressants (fluoxetine, paroxetine, imipramine, tranylcypromine, and deprenyl) significantly increased treatment response at 4–10 weeks compared with placebo (search date 2003, 4 double-blind RCTs, 662 people with depressive disorder or mixed episode disorder with at least 1 previous episode of mania; RR of response 1.9, 95% CI 1.5 to 2.3; NNT 4, 95% CI 3 to 7).

Tricyclic antidepressants versus selective serotonin reuptake inhibitors (SSRIs):
We found one systematic review. [36] It found that SSRIs increased clinical response at 4–10 weeks compared with tricyclic antidepressants; the increase was of borderline significance (search date 2003, 2 RCTs, 69 people; RR clinical response 1.67, 95% CI 1.00 to 2.78; P = 0.05). [36]

Adding antidepressants versus adding lithium or valproate:
We found one small RCT (27 people with mania or bipolar depression receiving lithium or valproate), which compared the addition of paroxetine versus the addition of a second dose of lithium or valproate. It found no significant difference between groups in depressive or manic symptoms over 6 weeks (results presented graphically). [37]

Moclobemide versus imipramine:
We found one double-blind RCT comparing moclobemide (450–750 mg/day) versus imipramine (150–250 mg/day) in 156 people with bipolar depression. [38] The primary outcome measure was improvement in the Hamilton Depression Rating Scale score. It found no significant difference between groups in mean improvement of the Hamilton Depression Rating Scale score (P value not reported). It also found no significant difference between groups in symptoms measured by the Montgomery–Asberg Scale, Clinical Global Impression, or in those responding to treatment (defined as reduction of at least 50% in the Hamilton Depression Rating Scale score and/or a final score of 10 or less). [38]

Harms: Antidepressants are associated with manic switching.

Antidepressants versus placebo:
The systematic review found no significant difference between antidepressants and placebo in the proportion of people switching to mania; however, it may have been underpowered to detect a clinically important difference (search date 2003, 5 RCTs; AR for manic switching: 11/287 [4%] with antidepressants *v* 23/492 [5%] with placebo; difference +0.9%, 95% CI –2% to +3.8%). [36]

Tricyclic antidepressants versus SSRIs:
The systematic review found that tricyclic antidepressants increased the proportion of people switching to mania compared with SSRIs, but the increase was not statistically significant (search date 2003, 3 RCTs: 6/74 [8%] with tricyclic antidepressants *v* 0/69 [0%] with SSRIs; RR 6.59, 95% CI 0.83 to 52.5). [36] However, the review may have been underpowered to detect a clinically important difference.

Moclobemide versus imipramine:
The RCT found that anticholinergic adverse effects were significantly more common with imipramine compared with moclobemide (dry mouth: 16% with moclobemide *v* 49% with imipramine; constipation: 5% *v* 17%; increased sweating: 4% *v* 11%; $P < 0.05$), and weight gain was also greater with imipramine, although this did not reach significance (mean: 0.1 kg loss with moclobemide *v* 1.2 kg gain with imipramine; P value not reported). Two people (4%) receiving moclobemide and six people (11%) receiving imipramine were withdrawn because of manic symptoms, with manic symptoms occurring earlier on imipramine, although these differences did not reach significance. [38]

Antidepressant adjunct to mood stabilisers:
We found one study of 159 people with bipolar type I disorder or bipolar type II disorder who participated in a total of 228 acute (10-week) drug exposures to bupropion, sertraline, or venlafaxine as an adjunct to a mood stabiliser. [39] The study reported each drug exposure as a "trial". People in 87 of these "trials" entered continuation treatment for up to 1 year. The study reported that threshold switches into full duration hypomania and mania occurred in 11% and 8% respectively of the acute treatment trials, and in 22% and 15% respectively of the continuation trials. It found that the rate of threshold switches was higher in the 169 trials in people with bipolar I disorder (31%) than in the 59 trials in people with bipolar type II disorder (19%). It concluded that adjunctive treatment with antidepressants in bipolar depression was associated with substantial risks of threshold switches to full duration hypomania or mania in both acute and long-term continuation treatment. Of the three included antidepressants, venlafaxine was associated with the highest relative risk of such switching, and bupropion with the lowest risk. [39] Limitations to the interpretation of this study include: the generalisability of data from the academically-based outpatient cohort to all people with bipolar disease; that 25% of people in the study had a history of rapid recycling; that some people were taking more than one antidepressant; and the lack of a placebo group. [39]

Suicidal ideation:
We found one cohort study which analysed the first 2000 people who completed 18 months' follow-up in a systematic treatment enhancement programme for bipolar disorder. [40] The study cohort comprised 425 people with a prospectively observed new-onset major depressive episode without suicidal ideation. Of these, 24 (6%) developed new onset suicidality, and two made suicide attempts. [40] The cohort found no association of new-onset suicidality with increased antidepressant exposure, or with the initiation of antidepressant treatment. However, these observations were based on only 24 people with new-onset suicidality.

Drug alert:
SSRIs have been linked to suicidal ideation in general (see reporting above). Other alerts and revised prescribing information regarding SSRIs include the increased risk of persistent pulmonary hypertension in infants born to women who had taken SSRIs during the latter half of pregnancy; the increased risk of congenital malformations in infants born to women taking paroxetine during the first trimester of pregnancy, and the potential for SSRIs to cause hyponatraemia, especially in elderly (see review on depression in adults: drug and physical treatments).

Comment: **Clinical guide:**
The evidence for treatment of unipolar depression (see review on depression in adults: drug and physical treatments) is believed to be applicable, although the efficacy of the treatments may be different, and specific adverse effects such as antidepressant-induced mania should be considered.

OPTION LITHIUM IN BIPOLAR DEPRESSION

We found no clinically important results about the effects of lithium in people with bipolar depression.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2000), which identified no RCTs of sufficient quality in people with bipolar depression. [41]

Harms: We found no good RCTs.

Comment: The systematic review identified one crossover trial in people with depression (52 people, 40 with bipolar depression). [41] Participants were randomised to 2 weeks of lithium and then crossed over to 6 days of placebo. The trial found that lithium improved symptoms in 32/40 (80%) people over 2 weeks, and that 12/32 (38%) of these relapsed when taking placebo. The trial found limited evidence that lithium did not induce more manic switching in bipolar depression than placebo.

OPTION CARBAMAZEPINE IN BIPOLAR DEPRESSION

We found no clinically important results about the effects of carbamazepine in people with bipolar depression.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2000), which identified no RCTs of sufficient quality in people with bipolar depression (see comment below). [41]

Harms: We found no good RCTs.

Comment: The review identified one crossover trial in people with depression (35 people, 24 with bipolar depression). [41] Participants were randomised to placebo before and after being crossed over to carbamazepine over 45 days. The trial found that carbamazepine improved symptoms in 62% of people over a mean 45 days.

OPTION VALPROATE IN BIPOLAR DEPRESSION

We found no clinically important results about the effects of valproate in people with bipolar depression.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found no systematic review or RCTs of valproate in people with bipolar depression.

Harms: We found no RCTs.

Comment: None.

OPTION LAMOTRIGINE IN BIPOLAR DEPRESSION

Symptoms of depression
Compared with placebo Lamotrigine may reduce symptoms, and increases the response rate compared with placebo after 7 weeks in people with bipolar type I disorder experiencing a depressive episode (moderate-quality evidence).

Adverse effects
Lamotrigine 200 mg has been associated with headaches.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2000), [41] which identified one RCT (195 people aged 19–75 years with bipolar type I disorder experiencing a major depressive episode). [42] The RCT compared three treatments: lamotrigine 200 mg daily, lamotrigine 50 mg daily, and placebo. [42] It found no significant difference between lamotrigine and placebo in Hamilton Depression Rating Scale score over 7 weeks, but found that lamotrigine 200 mg daily significantly improved Montgomery–Asberg Depression Rating Scale score (mean reduction: –13.3 with lamotrigine *v* –7.8 with placebo; $P < 0.05$) and increased the proportion of people who responded to treatment (measured by Clinical Global Impression Scale scores: mean change: 2.6 with lamotrigine *v* 3.3 with placebo; $P < 0.05$).

Harms: The RCT found that significantly more people had headache with lamotrigine 200 mg compared with placebo (20/63 [32%] with lamotrigine 200 mg *v* 11/65 [17%] with placebo; $P < 0.05$). [42]

Comment: None.

OPTION TOPIRAMATE IN BIPOLAR DEPRESSION

Symptoms of depression
Compared with bupropion Topiramate may be as effective as bupropion at reducing symptoms of depression in people also taking lithium or valproate after 8 weeks (low-quality evidence).

Note
We found no direct information about whether or not topicamate is better than no active treatment in people with bipolar depression.

Adverse effects
Topiramate is associated with a high rate of adverse effects including anxiety, increase or decrease in appetite, blurred vision, backache, headache, and nausea.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Topiramate versus placebo:
We found one systematic review (search date 2001), which identified no RCTs. [34]

Topiramate versus bupropion:
We found one systematic review, which identified no RCTs. [34] We found one subsequent RCT (36 people with bipolar depression, all taking lithium or valproate) comparing topiramate versus bupropion. [43] It found that both topiramate and bupropion significantly improved Clinical Global Impression scores from baseline at 8 weeks. It found no significant difference between treatments (P = 0.092; absolute numbers not reported).

Harms:

Topiramate versus placebo:
We found no RCTs. [34]

Topiramate versus bupropion:
The subsequent RCT found that 6/18 (33%) of people taking topiramate and 4/33 (22%) of people taking bupropion withdrew because of adverse effects, including anxiety, increase or decrease in appetite, blurred vision, backache, headache, and nausea (CI not reported). [43]

Comment: None.

OPTION QUETIAPINE IN BIPOLAR DEPRESSION New

Symptoms of depression
Compared with placebo Quetiapine reduces symptoms of depression compared with placebo after 8 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:
We found one RCT (542 people with bipolar type I [360 people] or bipolar type II [182 people] disorder experiencing a major depressive episode), which compared quetiapine (600 or 300 mg/day) versus placebo for 8 weeks. [44] The primary outcome was mean change in the Montgomery–Asberg Rating Scale score at 8 weeks. The RCT found that quetiapine at either dosage significantly improved Montgomery–Asberg Depression Rating Scale score compared with placebo at all weekly assessments (either dose of quetiapine *v* placebo; P < 0.001 at every weekly assessment from 1–8 weeks). [44] It found that quetiapine at either dosage significantly improved Montgomery–Asberg Depression Rating Scale score compared with placebo at 8 weeks (mean change from baseline to 8 weeks: –16.73 with quetiapine 600 mg/day *v* –16.39 with quetiapine 300 mg/day *v* –10.26 with placebo; either dose *v* placebo, P < 0.001). [44] The number of people completing the study at 8 weeks was 98/180 (54%) with quetiapine 600 mg daily, 121/181 (67%) with quetiapine 300 mg daily, and 107/181 (59%) with placebo. Analysis was by intention to treat with the last observation carried forward to the analysis.

Harms:
The RCT reported that treatment-emergent mania rates were low, and similar for the quetiapine and placebo groups (3.2% and 3.9%, respectively). [44] It found that, compared with placebo, quetiapine at either dose significantly increased dry mouth (41% with quetiapine 600 mg/day *v* 44% with quetiapine 300 mg/day *v* 8% with placebo), sedation (32% *v* 30% *v* 6%), somnolence (24% *v* 27% *v* 8%), dizziness (23% *v* 17% *v* 8%), and constipation (11% *v* 12% *v* 4%; all P values < 0.05).

Comment: None.

QUESTION What are the effects of interventions to prevent relapse of mania or bipolar depression?

OPTION COGNITIVE BEHAVIOURAL THERAPY TO PREVENT RELAPSE

Relapse
Compared with usual care Cognitive behavioural therapy may not reduce relapse rates compared with usual care after 12–18 months (moderate-quality evidence).

Adverse effects
The adverse effects of cognitive therapy are unclear.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2003, 3 RCTs reporting relapse, see comments), [45] one subsequent RCT [46] and one extended follow up report of one of the included RCTs. [47] The review did not perform a meta-analysis. In all three RCTs, cognitive therapy was adapted for bipolar disorder and included advice on medication compliance, self monitoring of symptoms, establishing routine, and ensuring sufficient sleep to reduce risk of relapse. The first RCT included in the review (42 outpatients aged 18 years or more with bipolar type I disorder who had experienced at least 1 episode of mania/hypomania or bipolar depression in the preceding 2 years, most taking lithium alone or in combination with another mood stabiliser) compared cognitive therapy versus usual care for 6 months followed by cognitive therapy. [48] It found no significant difference between cognitive therapy and usual care in the proportion of people who relapsed over 6 months, although fewer people receiving cognitive therapy relapsed (1/21 [5%] with cognitive therapy *v* 2/21 [10%] with usual care; P = 0.06). The RCT is likely to have been underpowered to detect a clinically important difference, and the overall the rate of relapse in this RCT was low. The second RCT (103 outpatients, aged 18–70 years with bipolar type I disorder not currently suffering from mania or bipolar depression, who had experienced 2 or more mood episodes in the preceding 2 years or 3 episodes in the preceding 5 years, all taking lithium, carbamazepine, or valproate sodium) compared cognitive therapy versus usual care for 1 year. [49] Cognitive therapy was given for 12–18 sessions over the first 6 months, followed by two additional sessions in the following 6 months. The RCT found that cognitive therapy significantly reduced the proportion of people who relapsed over 12 months (21/48 [44%] with cognitive therapy *v* 36/48 [75%] with usual care; HR 0.40, 95% CI 0.21 to 0.74). The third RCT (25 outpatients aged 18–70 years with bipolar type I disorder, not currently suffering from mania or bipolar depression, who had experienced 2 or more mood episodes in the preceding 2 years or 3 episodes in the last 5 years) compared 12–20 sessions of cognitive therapy versus routine care for 6 months (see comment below). [50] It found that cognitive therapy significantly reduced relapse over 6 months compared with usual care (RR 0.23, CI not reported; P < 0.001, absolute numbers not reported). We found one subsequent RCT involving 253 people with bipolar disorder, in which treatment as usual was compared with an additional 22 sessions of cognitive behavioural therapy plus treatment as usual. [46] People were assessed every 8 weeks for 18 months. The RCT found that more than half of participants had a recurrence by 18 months (53% with cognitive behavioural therapy *v* 51% with treatment as usual), but found no significant differences between groups (HR 1.05, 95% CI 0.74 to 1.50). A *post hoc* analysis found that adjunctive cognitive behavioural therapy was significantly more effective than treatment as usual in those with fewer than 12 previous episodes, but less effective in those with more episodes. [46] We found one extended follow-up [47] of an already reported RCT. [50] It presented an additional 18 months of follow-up data in addition to the initial 12 months follow-up of the original RCT. It found that, although the cognitive therapy plus usual care group exhibited significantly better mood ratings, social functioning, coping with bipolar prodromes, and dysfunctional goal attainment cognition compared with usual care alone, cognitive therapy had no significant effect in relapse reduction over the last 18 months of the study period. [47]

Harms: The first RCT identified by the review [45] found that there was one suicide in the people treated with cognitive therapy. [48] The review gave no information on adverse effects. [45] The subsequent RCT did not report on adverse effects. [46]

Comment: The systematic review also identified a fourth RCT (28 people taking lithium), which compared cognitive therapy with standard treatment for 6 weeks, but it only assessed compliance with lithium, and its reporting of results was unclear. [45]

OPTION EDUCATION TO RECOGNISE SYMPTOMS OF RELAPSE

Relapse of mania or depression
Compared with usual care Educational programmes to recognise symptoms of relapse may reduce relapse of mania, or overall relapse rates, over 18 months to 2 years compared with usual care (low-quality evidence).

Relapse of depression
The effects on relapse of depression of educational programmes compared with usual care are unclear (moderate-quality evidence).

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2003, 2 RCTs) and one subsequent RCT. [45] [51] The review did not conduct a meta-analysis. The first RCT included in the review (69 outpatients with bipolar disorder who had relapsed in the previous year) compared an educational programme to recognise symptoms of relapse versus treatment as usual over 18 months. [52] It found that people in the educational programme were significantly less likely to suffer a manic relapse over 18 months compared with people receiving usual care (9/33 [27%] with educational programme *v* 20/35 [57%] with usual care; RR 0.48, 95% CI 0.25 to 0.86; NNT 4, 95% CI 2 to 16), but may have been more likely to suffer from a depressive episode (18/33 [55%] with educational programme *v* 13/35 [37%] with usual care; RR 1.47, 95% CI 0.87 to 2.54), although the difference was not significant. It found that, compared with usual care, the educational programme significantly improved social function from baseline at 18 months (measured on a 4-point scale assessing 8 areas of social activity, where 0 = fair/good performance and 4 = inability to carry out function; mean difference in score 1.97, 95% CI 0.71 to 3.23). [52] The second RCT identified by the review compared group psychoeducation plus standard pharmacological treatment versus non-structured group meetings plus standard pharmacological treatment (control) for 14 weeks. [45] It found that the psychoeducational intervention significantly reduced recurrence at 2 years compared with control (single blind RCT, 120 people in remission with bipolar type I or type II disorder; recurrence during treatment: 38% with psychoeducation *v* 60% with control, P = 0.01; recurrence during follow-up: 67% with psychoeducation *v* 92% with control, P < 0.001). One subsequent RCT compared group psychoeducation plus standard pharmacological treatment versus non-structured group meetings plus standard pharmacological treatment (control) for 20 weeks. [51] It is not clear whether the people in this RCT were a subset of the people in the RCT with 120 people reported above. It found that the psychoeducational intervention significantly reduced recurrence and hospitalisations at 2 years compared with control (50 highly compliant people with bipolar type I disorder; recurrence defined as Young Mania Rating Scale score at least 12, AR: 15/25 [60%] with intervention *v* 23/25 [92%] with control, P < 0.01; hospitalisation: 2/25 [8%] with intervention *v* 9/25 [36%] with control, P = 0.01).

Harms: The review and the subsequent RCT gave no information on adverse effects. [45] [51] The first RCT identified by the review [45] found that, compared with usual care, education may increase depressive relapse (see benefits above). [52]

Comment: None.

OPTION FAMILY-FOCUSED PSYCHOEDUCATION TO PREVENT RELAPSE

Relapse
Compared with control interventions Family-focused psychoeducation may reduce relapse over up to 2 years compared with two family sessions plus crisis management or compared with individual-focused therapy (low-quality evidence).

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found no systematic review but found two RCTs (reported in three publications). [53] [54] [55] The first RCT (101 people with bipolar disorder who had recently recovered from an acute episode recruited from inpatient and outpatient facilities, all taking antipsychotic drugs) compared 21 sessions of family-focused psychoeducation versus two family sessions plus crisis management over 12 months. [53] Family-focused psychoeducation involved: education about the symptoms, causes, and treatment of bipolar disorder; education to recognise symptoms of relapse; preparation of a relapse prevention plan; and training in problem solving and communication skills. Crisis management involved emergency counselling sessions as needed, with a minimum of a monthly telephone call. The RCT found that family-focused psychoeducation significantly reduced the proportion of people who relapsed over 12 months compared with family session plus crisis management (HR 1.47, CI not reported; P = 0.042). [53] Interventions lasted for 9 months, and people remained on drug treatment for 2 years. Longer-term follow-up of this RCT showed that the significant reduction in relapse rate with family-focused psychoeducation was also present at 2 years (11/31 [35%] with family-focused psychoeducation *v* 38/70 [54%] with control; P < 0.005). [55] It found that family-focused psychoeducation significantly increased time to relapse compared with control (HR for relapse 0.38, 95% CI 0.20 to 0.75). The second RCT (53 people with bipolar type I disorder hospitalised after a manic episode, all taking lithium, valproate, carbamazepine, or a combination with or without antipsychotic or antidepressant drugs [not specified]) compared family-focused psychoeducation versus individual-focused therapy for 12 months' treatment. [54] It found no significant difference in the proportion of people who relapsed over the 12-month treatment period (46% with family fo-

cused psychoeducation *v* 52% with individual focused therapy; P = 0.11), although it found that family-focused psychoeducation significantly reduced relapse rates over 1 year after treatment (28% with family-focused psychoeducation *v* 60% with individual-focused therapy; P < 0.05).

Harms: The RCTs gave no information on adverse effects. [53] [54] [55]

Comment: None.

OPTION LITHIUM TO PREVENT RELAPSE

Relapse of mania
Compared with placebo Lithium reduces the rate of relapse of mania compared with placebo after 2 years (moderate-quality evidence).

Compared with olanzapine Lithium may be less effective at preventing relapse of mania compared with olanzapine after 52 weeks (low-quality evidence).

Relapse of depression
Compared with placebo Lithium does not reduce the rate of relapse of depression after 2 years compared with placebo (moderate-quality evidence).

Compared with olanzapine Lithium may be as effective as olanzapine at preventing relapse of depression after 52 weeks (low-quality evidence).

Relapse of mania or depression
Compared with valproate Lithium is as effective as valproate at reducing relapse rates after 12 months (high-quality evidence).

Compared with carbamazepine Lithium may be as effective as carbamazepine at reducing relapse rates after 2–3 years (low-quality evidence).

Compared with lamotrigine Lithium is as effective as lamotrigine at preventing relapse (high-quality evidence).

Compared with olanzapine Lithium is as effective as olanzapine at preventing relapse after 52 weeks (moderate-quality evidence).

Compared with antidepressants Lithium may be more effective than tricyclic antidepressants at preventing relapse after 1–2 years (low-quality evidence).

Adverse effects
Lithium is associated with adverse effects diarrhoea, somnolence, tremor, and hypothyroidism. Lithium may cause more adverse effects than carbamazepine or lamotrigine, and increases polyuria, thirst, and diarrhoea, but decreases sedation and infection rates, compared with valproate.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: **Lithium versus placebo:**
We found one systematic review in people with bipolar disorder, unipolar disorder, or mixed unipolar/bipolar disorder, [56] and three subsequent RCTs, two of which were analysed together in a pre-planned pooled analysis. [57] [58] The review (search date not stated, 5 RCTs, 770 people with bipolar disorder) found that lithium was more effective than placebo in preventing any relapse (RR 0.65, 95% CI 0.50 to 0.84) or manic relapse (RR 0.62, 95% CI 0.40 to 0.95). [56] Although there was a trend towards reduction of depressive relapses with lithium, this reduction did not reach significance (RR 0.72, 95% CI 0.49 to 1.07). The first two subsequent RCTs recruited people with bipolar type I disorder who had recently been depressed or manic, but had stabilised (Clinical Global Impression Severity of Illness score at least 3 for previous 4 weeks) after taking lamotrigine for 8 weeks. [57] The RCTs compared placebo, lithium (serum level of 0.8–1.1 mEq/L), and lamotrigine (50–400 mg/day fixed dose or 100–400 mg/day flexible dose) over 18 months. Pre-planned pooled analysis of these RCTs found that lithium significantly increased time to intervention for any mood episode compared with placebo (2 RCTs with 3 arms each, with 638 participants in total; median time to intervention: 184 days with lithium *v* 86 days with placebo; P < 0.001). Secondary analyses suggested that lithium protected against manic but not depressive relapse. The third subsequent RCT compared three treatments for up to 18 months: lithium (0.8–1.1 mEq/L), lamotrigine (50–400 mg/day), and placebo. [58] Only people who stabilised on lamotrigine after gradual withdrawal of concomitant drugs during an open-label run-in phase were included. It found that lithium significantly increased time to intervention for any mood episode compared with placebo

(463 currently or recently depressed people with bipolar disorder, median for any mood episode: 170 days with lithium *v* 93 days with placebo; P = 0.029).

Lithium versus valproate:
We found one systematic review (search date not reported), which identified one RCT (372 people) comparing three treatments: lithium, valproate, and placebo. [59] It found no significant difference between lithium and valproate in relapse at 12 months (relapse defined as withdrawal caused by an episode of bipolar disorder: 12/187 [6%] with lithium *v* 9/91 [10%] with valproate; RR 0.8, 95% CI 0.5 to 1.2), but it is likely to have been too small to detect a clinically important difference.

Lithium versus carbamazepine:
We found one systematic review [60] (search date not reported, 10 RCTs, 572 people with unipolar or bipolar disorder) and one subsequent RCT [61] comparing lithium versus carbamazepine. The review found no significant difference between lithium and carbamazepine in the proportion of people who relapsed over 1–3 years (60% with lithium *v* 55% with carbamazepine; reported as non-significant; no further data reported; see comment below). [60] The subsequent RCT (94 outpatients aged 18 years and over with bipolar disorder, who had experienced at least 2 mood episodes in the preceding 3 years) compared lithium (blood level 0.6–1.0 mmol/L) versus carbamazepine (blood level 6–10 mg/L) for 2 years of treatment. [61] It found no significant difference between lithium and carbamazepine in the proportion of people who relapsed over 2 years (relapse defined as developing an episode of mania or bipolar depression: 12/44 [27%] with lithium *v* 21/50 [42%] with carbamazepine; RR 1.54, 95% CI 0.88 to 2.78). A pre-planned subgroup analysis suggested that lithium was more effective in people who were randomised when euthymic.

Lithium versus lamotrigine:
We found no systematic review but found three RCTs, two of which were analysed together in a pre-planned pooled analysis. [57] [58] The first two subsequent RCTs were in people with bipolar type I disorder who had recently been depressed or manic, but had stabilised after taking lamotrigine for 8 weeks (see benefits of Lithium versus placebo above for details). [57] Pooled analysis of these two RCTs found no significant difference between lithium and lamotrigine in the time to intervention for any mood episode (638 people; median survival: 184 days *v* 197 days with lamotrigine; P = 0.63). Secondary analysis found that lithium reduced manic relapse compared with lamotrigine (P = 0.03). The third RCT (463 people) compared three treatments: lithium, lamotrigine, and placebo (see benefits of Lithium versus placebo above for details). [58] It found no significant difference between lithium and lamotrigine for time to intervention for any mood episode (median: 170 days with lithium *v* 200 days with lamotrigine; P = 0.92). [58]

Lithium versus olanzapine:
See benefits of olanzapine, p 28 to prevent relapse.

Lithium versus antidepressants:
See benefits of antidepressants to prevent relapse, p 28 .

Harms:

Lithium versus placebo:
The systematic review found that overall withdrawals were less common with lithium than with placebo (absolute figures not reported; RR 0.86, 95% CI 0.80 to 0.93). [56] Lithium significantly increased diarrhoea (RR 2.35, 95% CI 1.35 to 4.10), nausea (RR 1.76, 95% CI 1.07 to 2.92), and somnolence (RR 1.93, 95% CI 1.02 to 3.84) compared with placebo. There was an increase in hypothyroidism with lithium compared with placebo, but this did not reach significance (RR 9.26, 95% CI 0.03 to 169.91). The pooled analysis of two RCTs comparing lithium, lamotrigine, and placebo found no evidence that lithium caused affective switch. [57] It found that lithium significantly increased withdrawal caused by adverse effects compared with placebo (30/167 [18%] with lithium *v* 15/191 [8%] with placebo; P < 0.01). Compared with placebo, lithium also significantly increased nausea (20% *v* 11%; P < 0.05), somnolence (13% *v* 7%; P < 0.05), diarrhoea (19% *v* 8%; P < 0.05), and tremor (15% *v* 5%; P < 0.05). The subsequent RCT (463 people) found no significant difference between lithium and placebo in withdrawal caused by adverse effects (16% with lithium *v* 10% with placebo; P = 0.076). [58] The most common adverse effect was headache, but the incidence was similar for lithium and placebo (19% with lithium *v* 21% with placebo; P value not reported). It found that lithium increased somnolence and tremor compared with placebo (somnolence: 13% with lithium *v* 6% with placebo; tremor: 17% with lithium *v* 5% with placebo; P < 0.05 for both).

Lithium versus valproate:
The review found that valproate was significantly more likely than lithium to cause sedation (1 RCT: 78/187 [42%] with valproate *v* 24/91 [26%] with lithium; RR 1.6, 95% CI 1.1 to 2.3) and infection (type of infection not specified, 1 RCT: 51/187 [27%] with valproate *v* 12/91 [13%] with lithium; RR 2.1, 95% CI 1.2 to 3.7), but significantly less likely to cause polyuria (15/187 [8%] with valproate *v* 17/91 [19%] with lithium; RR 0.4, 95% CI 0.2 to 0.8), thirst (11/187 [6%] with valproate *v* 14/91

[15%] with lithium; RR 0.4, 95% CI 0.2 to 0.8), and possibly diarrhoea (65/187 [35%] with valproate *v* 42/91 [46%] with lithium; RR 0.75, 95% 0.6 to 1.0). [59]

Lithium versus carbamazepine:
The review gave no information on adverse effects. [60] One RCT (144 people with bipolar disorder) identified by the review found that, although more people taking carbamazepine than taking lithium withdrew from the trials (9/70 [13%] with carbamazepine *v* 4/74 [5%] with lithium; reported as non-significant; no further data reported), a significantly higher proportion of people taking lithium compared with carbamazepine had "slight or moderate" adverse effects over 2.5 years (21% with carbamazepine *v* 61% with lithium; P < 0.001). [62] The subsequent RCT found that blurred vision, difficulty concentrating, thirst, hand tremor, and muscle weakness were more common with lithium than with carbamazepine. [61] Increased appetite was more common with carbamazepine.

Lithium versus lamotrigine:
The pooled analysis of two RCTs found that lithium significantly increased withdrawal caused by adverse effects compared with lamotrigine (30/167 [18%] with lithium *v* 23/280 [8%] with lamotrigine; P < 0.01). It found that lithium significantly increased diarrhoea (19% with lithium *v* 7% with lamotrigine; P < 0.05) and tremor (15% with lithium *v* 4% with lamotrigine; P < 0.05) compared with lamotrigine. [57] There was no evidence that either active treatment caused affective switch. The second RCT found that lithium significantly increased diarrhoea and tremor compared with lamotrigine (diarrhoea: 16% with lithium *v* 7% with lamotrigine; tremor: 17% with lithium *v* 5% with lamotrigine; P < 0.05 for both). [58]

Lithium versus olanzapine:
See harms of olanzapine, p 28 .

Comment:

Lithium versus carbamazepine:
The results of the review should be interpreted with caution because it combined trials of unipolar and bipolar disorder. [60]

OPTION VALPROATE TO PREVENT RELAPSE

Relapse
Compared with placebo Valproate may reduce relapse rates after 12 months compared with placebo (low-quality evidence).

Compared with lithium Valproate is as effective as lithium at reducing relapse rates after 12 months (high-quality evidence).

Adverse effects
Valproate has been associated with tremor, weight gain, and alopecia. It may cause more sedation and infection than lithium, but less polyuria, thirst, and diarrhoea.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Valproate versus placebo:
We found one systematic review (search date not reported, 1 RCT, 372 people with bipolar disorder) comparing valproate, lithium, and placebo. [59] It found that valproate significantly reduced relapse over 12 months compared with placebo (relapse defined as withdrawal because of an episode of bipolar disorder: 45/187 [24%] with valproate *v* 36/94 [38%] with placebo; RR 0.6, 95% CI 0.4 to 0.9), but found no significant difference in time to relapse (P = 0.33; no further data reported).

Valproate versus lithium:
See benefits of lithium, p 19 .

Harms:

Valproate versus placebo:
The review found that valproate was significantly more likely than placebo to cause tremor (RR 3.2, 95% CI 1.9 to 5.6), weight gain (RR 2.9, 95% 1.3 to 6.2), alopecia (RR 2.4, 95% CI 1.1 to 5.7), and nausea (RR 1.4, 95% CI 1.0 to 1.9). [59] We also found one case control study (32 women aged 15–45 years with bipolar disorder), which found that 8/17 (47%) women taking valproate had current menstrual irregularities compared with 2/15 (13%) women not taking valproate. [64]

Valproate versus lithium:
See harms of lithium, p 24 .

Comment: None.

OPTION CARBAMAZEPINE TO PREVENT RELAPSE

Relapse
Compared with placebo Carbamazepine may be no more effective than placebo at preventing relapse after 1 year (low-quality evidence).

Compared with lithium Carbamazepine may be as effective as lithium at reducing relapse rates after 2–3 years (low-quality evidence).

Adverse effects
Carbamazepine has been associated with fewer adverse effects than lithium.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Carbamazepine versus placebo:
We found one systematic review (search date not stated), which identified one RCT. [65] The small RCT identified by the review (22 people during remission of bipolar disorder) found no significant difference in effectiveness between carbamazepine and placebo at 1 year (effectiveness not further defined in the review; AR: 60% with carbamazepine *v* 22% with placebo; P < 0.10). The RCT may have been too small to detect a significant difference.

Carbamazepine versus lithium:
See benefits of lithium, p 24 .

Harms:

Carbamazepine versus placebo:
The review (search date not stated) did not report on harms. [65]

Carbamazepine versus lithium:
See harms of lithium, p 24 .

Comment:

A systematic review of the effects of carbamazepine in preventing relapse is in progress. [66]

OPTION LAMOTRIGINE TO PREVENT RELAPSE

Relapse
Compared with placebo Lamotrigine may reduce relapse rates compared with placebo after 18 months (low-quality evidence).

Compared with lithium Lamotrigine is as effective as lithium at preventing relapse (high-quality evidence).

Adverse effects
Lamotrigine has been associated with headaches and rashes, but may be less likely than lithium to cause diarrhoea.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Lamotrigine versus placebo:
We found no systematic review but found four RCTs, two of which were analysed together in a pre-planned pooled analysis. [57] [58] [67] The first two RCTs recruited recently depressed or manic people with bipolar type I disorder who had stabilised (Clinical Global Impression Severity of Illness score at least 3 for previous 4 weeks) after taking lamotrigine for 8 weeks. [57] Pooled analysis of these RCTs found that lamotrigine delayed time to intervention for any mood episode compared with placebo (median survival: 197 days with lamotrigine *v* 86 days with placebo; P < 0.05). The third RCT (182 people with rapid cycling bipolar disorder (see table 1, p 33) found no significant difference between lamotrigine and placebo in the time to requiring additional medication (P = 0.177, results presented graphically). [67] The fourth subsequent RCT (463 currently or recently depressed people) compared three treatments for up to 18 months: lithium (0.8–1.1 mEq/L), lamotrigine (50–400 mg/day), and placebo. [58] It found that lamotrigine significantly increased time to intervention for any mood episode compared with placebo (median for any mood episode: 200 days with lithium *v* 93 days with placebo; P = 0.029). [58]

Lamotrigine versus lithium:
See benefits of lithium, p 24 .

Harms:

Lamotrigine versus placebo:
The pooled analysis of two RCTs found no evidence that lamotrigine caused affective switch. [57] It found no difference between lamotrigine and placebo for withdrawal caused by adverse effects, headache, nausea, somnolence, or diarrhoea (withdrawal: 23/280 [8%] with lamotrigine *v* 15/191

[8%] with placebo; headache: 19% *v* 19%; nausea: 14% *v* 11%; somnolence: 9% *v* 7%; diarrhoea: 7% *v* 8%; reported as non-significant, figures not reported). The second RCT found no significant difference between lamotrigine and placebo in the proportion of people who had adverse effects, including nausea and headache (67% with lamotrigine *v* 68% with placebo; reported as non-significant, CI not reported). [66] The third RCT found that lamotrigine significantly increased rash compared with placebo (rash: 7% with lamotrigine *v* 2% with placebo; P < 0.05). [58] The proportion of people with headache and nausea was similar for lamotrigine and placebo (headache: 18% with lamotrigine *v* 21% with placebo; nausea: 17% with lamotrigine *v* 12% with placebo; P values not reported).

Lamotrigine versus lithium:
See harms of lithium, p 24 .

Comment: None

OPTION ANTIDEPRESSANTS TO PREVENT RELAPSE

Relaspe
Compared with placebo Tricyclic antidepressants may not reduce relapse rates after 1–2 years compared with placebo (low-quality evidence).

Compared with lithium Tricyclic antidepressants may be less effective than lithium at preventing relapse after 1–2 years (low-quality evidence).

Adverse effects
Antidepressants may induce mood instability or manic episodes.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits: We found one systematic review (search date 2000; 4 RCTs, 258 people with bipolar type I or type II disorder) comparing tricyclic antidepressants versus placebo or lithium. [68] The review did not perform a meta-analysis or quantify its conclusions. It provided a narrative overview of the studies, and found no clear evidence that tricyclic antidepressants reduce relapse over 1–2 years compared with placebo. It suggested that tricyclic antidepressants may be less effective in preventing relapse over 1–2 years than lithium.

Harms: The review suggested that antidepressants may induce mood instability or manic episodes. [68]

Comment: None.

OPTION OLANZAPINE TO PREVENT RELAPSE New

Relapse of mania or depression
Compared with placebo Olanzapine reduces the rate of relapse after 48 weeks compared with placebo (moderate-quality evidence).

Compared with placebo as adjunct treatment The effect, after 18 months, of adding olanzapine to lithium or valproate mood stabiliser treatment is unclear compared with adding placebo (very low-quality evidence).

Compared with lithium Olanzapine is as effective as lithium at preventing overall relapse of bipolar disorder after 52 weeks (moderate-quality evidence).

Relapse of mania
Compared with lithium Olanzapine may be more effective than lithium at preventing relapse of mania (low-quality evidence).

Relapse of depression
Compared with lithium Olanzapine may be as effective as lithium at preventing relapse of depression (low-quality evidence).

Adverse effects
Olanzapine has been associated with weight gain.

For GRADE evaluation of interventions for bipolar disorder, see table, p 34 .

Benefits:

Olanzapine versus placebo:
We found one double-blind RCT (361 people) in which people achieving symptomatic remission from a manic or mixed episode of bipolar type I disorder following 6–12 weeks of open-label acute treatment with 5–20 mg daily of olanzapine were randomly assigned in a 2:1 ratio to double-blind maintenance treatment with olanzapine (225 people) or placebo (136 people) for up to 48 weeks. [69] The primary outcome was time to symptomatic relapse into any mood disorder. The RCT found that olanzapine significantly increased the time to relapse compared with placebo (median: 174 days with olanzapine *v* 22 days with placebo; P < 0.001), and significantly decreased the proportion of people with symptomatic relapse into any mood disorder compared with placebo (105/225 [47%] with olanzapine *v* 109/136 [80%] with placebo; OR 4.61, 95% CI 2.81 to 7.58). [69]

Olanzapine plus mood stabiliser versus mood stabiliser alone:
We found one RCT (99 people) in which bipolar patients achieving syndromic remission after 6 weeks' treatment with olanzapine plus either lithium (0.6–1.2 mmol/L) or valproate (50–125 microg/ml) were randomised to receive lithium or valproate plus either olanzapine 5–20 mg daily or placebo. [70] They were followed in a double-blind trial for 18 months. [70] The RCT defined syndromic relapse as meeting *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) criteria for a manic mixed, or depressive episode, and symptomatic relapse by using the total score on the Young Mania Rating Scale (15 or greater) and the 21-item Hamilton Rating Scale for Depression (15 or greater). The RCT found that the treatment difference in time to relapse into either mania or depression was not significant between groups for syndromic relapse (median time to relapse: 94 days with olanzapine plus mood stabilisers *v* 40.5 days with placebo plus mood stabilisers; P = 0.742), but was significant for symptomatic relapse (163 days *v* 42 days; P = 0.023). [70]

Olanzapine versus lithium:
We found one RCT (431 people) of bipolar patients receiving open-label co-treatment with olanzapine and lithium for 6–12 weeks. [63] Those meeting symptomatic remission criteria were randomly assigned to 52 weeks of double-blind monotherapy with olanzapine (5–20 mg/day; 217 people) or lithium (target blood level 0.6–1.2 meq/L; 214 people). The RCT found that symptomatic relapse/recurrence (score 15 or more on the Young Mania Rating Scale or Hamilton depression scale) occurred in 65/217 (30%) of olanzapine treated people compared with 83/214 (39%) of lithium treated people (P = 0.055). In a subgroup analysis, the RCT found that, compared with lithium, olanzapine had significantly lower risks of manic episode and mixed episode relapse/recurrence (mania, P < 0.02; mixed, P < 0.005), but found no significant difference between groups in depression recurrence (P = 0.15).

Harms:

Olanzapine versus placebo:
The RCT reported that during the open-label phase, people gained a mean of 3 kg in weight. [69] After randomisation, people with placebo lost a mean of 2 kg, whereas those on olanzapine gained an additional 1 kg. We found one further analysis of a 3-week RCT of olanzapine for people with mania, which was then followed by open continuation treatment with olanzapine for up to a year. [71] Among 113 people treated with olanzapine for a mean of 28 weeks, body mass index (BMI) increased from a baseline mean of 28.8 kg/m^2, by 7.9% (P < 0.001), into the obese range (31.0 kg/m^2). It found that BMI increased significantly more among 40 people achieving symptomatic recovery than in the 73 who did not (P = 0.004). It reported that, on average, serum cholesterol increased 4.8 times more (18% *v* 4%; P = 0.002) and endpoint cholesterol levels were greater (risk of total serum cholesterol newly 240 mg/dL or more: RR 3.6, 95% CI 1.5 to 8.0) in people with above average BMI gain, and this group also experienced significantly larger increases in systolic and diastolic blood pressure, pulse rates, and non-fasting serum glucose than people who had low BMI gain. [71]

Olanzapine plus mood stabiliser versus mood stabiliser alone:
The RCT found a similar incidence of adverse effects between groups, with the exception of insomnia (4% of people in olanzapine group *v* 27% of people in mood-stabilisers-alone group; risk difference –23.2, 95% CI –36.8 to –9.5) and weight gain (20% of people in olanzapine group *v* 6% of people in mood-stabilisers-alone group; risk difference 13.4, 95% CI 0.5 to 26.2). [70]

Olanzapine versus lithium:
The RCT reported that, compared with lithium, olanzapine significantly increased depression (21% with olanzapine *v* 12% with lithium; P = 0.01) and hypersomnia (3% *v* 0%; P = 0.03), and deceased insomnia (8% *v* 22%; P < 0.001), worsening of mania (8% *v* 21%, P < 0.001), and nausea (0.5% *v* 3.7%; P = 0.02). [63] It found that mean weight gain during open-label co-treatment was 2.7 kg; during double-blind monotherapy, weight gain was significantly greater with olanzapine than with lithium (mean: +1.8 kg with olanzapine *v* –1.4 kg with lithium; P < 0.001). [63]

Comment:

None.

GLOSSARY

Cognitive therapy Brief (20 sessions over 12–16 weeks) structured treatment aimed at changing the dysfunctional beliefs and negative automatic thoughts that characterise depressive disorders. It requires a highly trained therapist.
Manic switching involves onset of a manic episode shortly after treatment for a depressive episode. It may be more likely after treatment with antidepressants.
Relapse A return of symptoms to the extent that the disorder again meets criteria for the full syndromes. In practice, people with bipolar disorder learn to recognise early warning signs and begin treatment before criteria are met. For this reason, relapse is often pragmatically defined as the need for drug treatment due to re-emergence of depressive or manic symptoms.
Young Mania Rating Scale (YMRS) is a checklist of 11 manic symptoms, rated on a scale of 0–4 (7 symptoms) or 0–8 (4 symptoms); a higher score indicates greater symptom severity. Individual scores are summed to give a total score of 0–60. The scale was designed to be administered by clinicians and to measure the severity of manic symptoms, and to be sensitive to the effects of treatments on manic symptoms. The items were selected based on the core symptoms of mania and were developed to follow the style of the Hamilton Depression Rating Scale.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Quetiapine in bipolar depression.
New option added Olanzapine to prevent relapse.
Antidepressants (under question on treatments for bipolar depression) One RCT added in benefits section, [38] two studies added to harms section, [39] [40] and harms data enhanced. Categorisation unchanged (Likely to be beneficial).
Carbamazepine (under question on treatments in mania) One RCT added; [29] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).
Cognitive behaviour therapy (under question on treatments to prevent relapse) One subsequent RCT [46] and one extended follow-up of an already reported RCT added; [47] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).
Haloperidol (under question on treatments in mania) One systematic review [18] and one RCT added; [16] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).
Lithium (under question on treatments in mania) Two RCTs added; [10] [11] benefits and harms data enhanced, categorisation unchanged (Beneficial).
Lithium (under question on treatments to prevent relapse) One RCT added; [63] benefits and harms data enhanced, categorisation unchanged (Beneficial).
Valproate (under question on treatments in mania) One RCT [14] and one observational study added; [13] benefits and harms data enhanced, categorisation unchanged (Beneficial).
Ziprasidone (under question on treatments in mania) One RCT added; [26] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).
Quetiapine (under question on treatments in mania) Three RCTs added; [10] [14] [16] benefits and harms data enhanced, categorisation changed from Unknown effectiveness to Likely to be beneficial.
Risperidone (under question on treatments in mania) One systematic review, [18] one subsequent report of an RCT included in the systematic review, [19] and one subsequent RCT added; [20] benefits and harms data enhanced, categorisation changed from Likely to be beneficial to Beneficial.
Topiramate (under question on treatments in mania) One report including four double-blind RCTs added; [11] benefits and harms data enhanced, categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

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Disclaimer

TABLE 1 **DSM-IV classification of bipolar disorders (see text). Reprinted with permission from Elsevier.** [1]

DSM IV Category	Criteria	Course specifiers and examples
Bipolar I disorder	One or more manic or mixed episodes, usually accompanied by one or more major depressive episodes	To describe current (or most recent episode): mild, moderate, severe without psychotic features; severe with psychotic features; in partial or full remission; with catatonic features; with postpartum onset
		To describe current (or most recent) major depressive episode: chronic; with melancholic features; with atypical features
		To describe pattern of episodes: with or without full interepisode recovery; with seasonal pattern; with rapid cycling (> 4 episodes in previous 12 months)
Bipolar II disorder	Recurrent major depressive episodes with one or more hypomanic (milder than manic) episodes	To describe current (or most recent episode): hypomanic; depressed
		To describe current (or most recent) major depressive episode and pattern of episodes: see bipolar I disorder
Cyclothymic disorder	Chronic (> 2 years), fluctuating mood disturbance involving numerous periods of mild hypomanic and depressive symptoms that do not meet criteria for a major depressive episode	Over 2 years any symptom free intervals last no longer than 2 months
Bipolar disorder (not otherwise specified)	Disorders with bipolar features that do not meet criteria for any specific bipolar disorder	Examples: very rapid cycling (over days); recurrent hypomanias without depressive symptoms; indeterminate whether primary or secondary (due to a general medical condition or substance abuse)

TABLE **GRADE evaluation of interventions for bipolar disorder**

Important outcomes	Symptoms, remission, relapse, suicide, social/occupational functioning, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments in people with mania associated with bipolar disorder?									
2 (412) [7] [10]	Symptoms of mania	Lithium *v* placebo	4	0	0	0	0	High	
4 (114) [7]	Remisison of mania	Lithium *v* chlorpromazine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertain definition of outcome
2 (50) [7]	Symptoms of mania	Lithium *v* haloperidol	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (54) [7]	Symptoms of mania	Lithium *v* risperidone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (30) [8]	Symptoms of mania	Lithium *v* olanzapine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (158) [6]	Symptoms of mania	Lithium *v* valproate	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (176) [7]	Symptoms of mania	Lithium *v* carbamazepine	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for range of outcomes
1 (30) [9]	Symptoms of mania	Lithium *v* lamotrigine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (344) [23]	Symptoms of mania	Lithium or valproate plus olanzapine *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for range of interventions
1 (302) [10]	Symptoms of mania	Lithium *v* quetiapine	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (336) [11]	Symptoms of mania	Lithium *v* topiramate	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (316) [6]	Symptoms of mania	Valproate *v* placebo	4	0	0	0	0	High	
1 (36) [6]	Symptoms of mania	Valproate *v* haloperidol	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (611) [6] [4]	Symptoms of mania	Valproate *v* olanzapine	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
2 (59) [6]	Symptoms of mania	Valproate *v* carbamazepine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (50) [14]	Symptoms of mania	Valproate *v* quetiapine	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up
1 (13) [15]	Symptoms of mania	Chlorpromazine *v* imipramine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (302) [16]	Symptoms of mania	Haloperidol v placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
1 (302) [16]	Symptoms of mania	Haloperidol *v* quetiapine	4	–2	0	0	0	Low	Quality point deducted for poor follow-up and post hoc comparison between active treatments
1 (297) [18]	Symptoms of mania	Haloperidol *v* risperidone	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
1 (219) [4]	Symptoms or relapseof mania	Haloperidol *v* olanzapine	4	0	0	0	0	High	
3 (827) [18] [19] [20]	Symptoms of mania	Risperidone *v* placebo	4	0	0	0	0	High	

Important outcomes	Symptoms, remission, relapse, suicide, social/occupational functioning, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (238) [18]	Symptoms of mania	Risperidone *v* placebo (adjunct to lithium or anticonvulsants)	4	0	0	0	0	High	
3 (455) [23] [24]	Symptoms of mania	Olanzapine *v* placebo	4	0	0	0	–1	Moderate	Directness point deducted for differences in endpoints
2 (403) [25] [26]	Symptoms of mania	Ziprasidone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
1 (30) [14]	Symptoms of mania	Quetiapine plus valproate *v* placebo plus valproate	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (604) [16] [10]	Symptoms of mania	Quetiapine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
2 (443) [28] [29]	Symptoms of mania	Carbamazepine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
1 (30) [30]	Symptoms of mania	Clonazepam *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (117) [32]	Symptoms of mania	Gabapentin *v* placebo (adjunct therapy)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
5 (1185) [33] [11]	Symptoms of mania	Topiramate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments in bipolar depression?									
4 (662) [36]	Symptoms of depression	Antidepressants *v* placebo	4	0	0	0	0	High	
2 (69) [36]	Symptoms of depression	Tricyclic antidepressants *v* selective serotonin reuptake inhibitors	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (27) [37]	Symptoms of depression	Paroxetine plus lithium or valproate *v* second dose of lithium or valproate	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (156) [38]	Symptoms of depression	Moclobemide *v* imipramine	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
5 (779) [36]	Manic switching	Antidepressants *v* placebo	4	0	0	0	0	High	
3 (143) [36]	Manic switching	Tricyclic antidepressants *v* selective serotonin reuptake inhibitors	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (195) [41]	Symptoms of depression	Higher-dose lamotrigine *v* lower-dose lamotrigine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data. Consistency point deducted for conflicting results but added for evidence of dose response
1 (36) [43]	Symptoms of depression	Topiramate *v* bupropion	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (542) [44] [Calabrese 2005]	Symptoms of depression	Quetiapine *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor follow-up
What are the effects of interventions to prevent relapse of mania or bipolar depression?									
4 (423) [48] [49] [50] [46] [47]	Relapse	Cognitive behavioural therapy *v* usual care	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results

Important outcomes	Symptoms, remission, relapse, suicide, social/occupational functioning, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (189) [52] [45] [72]	Relapse of mania or depression	Education to recognise symptoms of relapse *v* usual care	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of different interventions
1 (69) [52]	Relapse of depression	Education to recognise symptoms of relapse *v* usual care	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (154) [53] [54] [55]	Relapse	Family-focused psychoeducation *v* control	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
8 (1871) [56] [57] [58]	Relapse of mania	Lithium *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for outcome assessment being a subgroup analysis
8 (1871) [56] [57] [58]	Relapse of depression	Lithium *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for outcome assessment being a subgroup analysis
1 (327) [6] [Macritchie nd]	Relapse	Lithium *v* valproate	4	0	0	0	0	High	
11 (666) [60] [61]	Relapse	Lithium *v* carbamazepine	4	–1	0	-1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of people with unipolar disorder
3 (1101) [57] [58]	Relapse	Lithium *v* lamotrigine	4	0	0	0	0	High	
1 (431) [63]	Relapse (mania or depression)	Lithium *v* olanzapine	4	0	0	–1	0	Moderate	Directness point deducted for selection of responders for inclusion
1 (431) [63]	Relapse of mania	Lithium *v* olanzapine	4	0	0	–2	0	Low	Directness point sdeducted for selection of responders for inclusion and for assessment of outcome as subgroup analysis
1 (431) [63]	Relapse of depression	Lithium *v* olanzapine	4	0	0	–2	0	Low	Directness point deducted for selection of responders for inclusion and for assessment of outcome as subgroup analysis
1 (372) [6]	Relapse	Valproate *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (22) [65]	Relapse	Carbamazepine *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertain outcome
4 (1283) [57] [58] [67]	Relapse	Lamotrigine *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
4 (258) [68]	Relapse	Antidepressants *v* placebo v lithium	4	–2	0	0	0	Low	Quality point deducted for non-systemic review and incomplete reporting of results
1 (361) [69]	Relapse	Olanzapine *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion only of responders

Important outcomes	Symptoms, remission, relapse, suicide, social/occupational functioning, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (99) [70]	Relapse	Olanzapine plus mood stabiliser *v* mood stabiliser plus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for conflicting results. Directness point deducted for inclusion only of responders

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.